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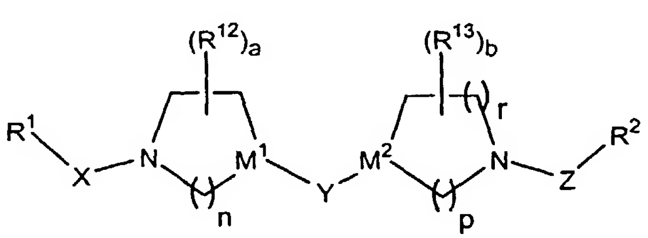
(54) Title: NOVEL NON-IMIDAZOLE COMPOUNDS



(I)

(57) Abstract: Disclosed are novel compounds of the formula (I). Also disclosed are pharmaceutical compositions comprising the compounds of Formula (I). Also disclosed are methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I). Also disclosed are methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I) in combination with a H1 receptor antagonist.

NOVEL NON-IMIDAZOLE COMPOUNDS

BACKGROUND OF THE INVENTION

WO 95/14007 published May 26, 1995 discloses H_3 receptor antagonists of the imidazole type.

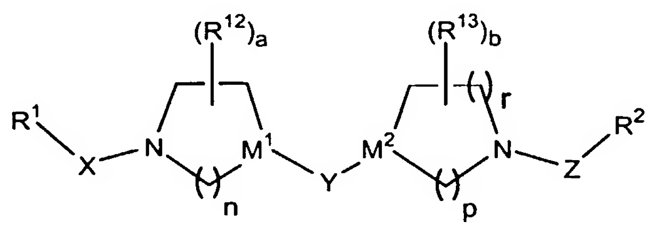
WO99/24405 published May 20, 1999 discloses H_3 receptor ligands of the imidazole type.

US 5,869,479 issued February 9, 1999 discloses compositions for the treatment of the symptoms of allergic rhinitis using a combination of at least one histamine H_1 receptor antagonist and at least one histamine H_3 receptor antagonist.

In view of the art's interest in compounds which affect H_3 receptors, novel compounds that are antagonists of H_3 receptors would be a welcome contribution to the art. This invention provides just such a contribution.

Summary of the Invention

The present invention provides novel compounds of structure I.



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) R^1 is selected from:

(1) aryl;

(2) heteroaryl;

(3) heterocycloalkyl

(4) alkyl;

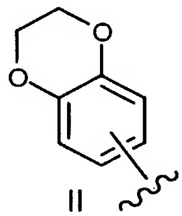
(5) $-C(O)N(R^{4B})_2$;

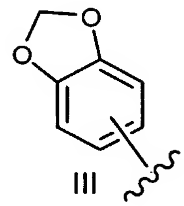
(6) cycloalkyl;

(7) arylalkyl;

(8) heteroarylheteroaryl (e.g., isoxazoylthienyl or pyridylthienyl); or

(9) a group selected from:


II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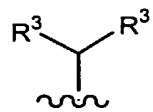
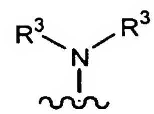
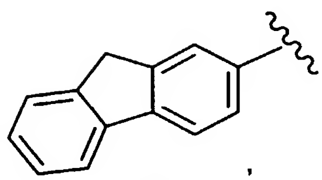
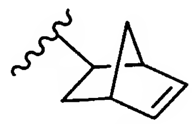


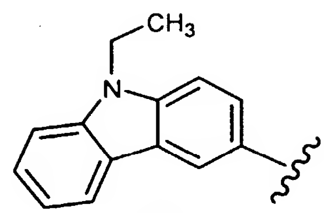
IV ,



IVA ,


IVB ,


IVC , or



IVD ;

said aryl (see (A)(1) above), heteroaryl (see (A)(2) above), aryl portion of arylalkyl (see (A)(7) above), phenyl ring of formula II (see (A)(9) above), phenyl ring of formula III (see (A)(9) above), phenyl rings of formula IVB (see (A)(9) above), or phenyl rings of formula IVD (see (A)(9) above) are optionally substituted with 1 to 3 substituents independently selected from:

(1) halogen (e.g., Br, F, or Cl, preferably F or Cl);

(2) hydroxyl (i.e., -OH);

(3) lower alkoxy (e.g., C_1 to C_6 alkoxy, preferably C_1 to C_4 alkoxy, more preferably C_1 to C_2 alkoxy, most preferably methoxy);

(4) -Oaryl (i.e., aryloxy);

(5) $-SR^{22}$;

(6) $-CF_3$;

(7) $-OCF_3$;

(8) $-OCHF_2$;

(9) $-NR^4R^5$;

(10) phenyl;

(11) NO_2,

(12) $-CO_2R^4$;

(13) $-CON(R^4)_2$ wherein each R^4 is the same or different;

(14) $-S(O)_2R^{22}$;

(15) $-S(O)_2N(R^{20})_2$ wherein each R^{20} is the same or different;

(16) $-N(R^{24})S(O)_2R^{22}$;

(17) -CN;

(18) $-CH_2OH$;

(19) $-OCH_2CH_2OR^{22}$;

(20) alkyl (e.g., C_1 to C_4, such as methyl);

(21) substituted phenyl wherein said phenyl has 1 to 3 substituents independently selected from alkyl, halogen, -CN, $-NO_2$, $-OCHF_2$, -Oalkyl;

(22) -Oalkylaryl (preferably –Oalkylphenyl or –Oalkyl-substituted phenyl, e.g., $-OCH_2$dichlorophenyl, such as $-OCH_2$-2,6-dichlorophenyl or $-OCH_2$-2-chloro-6-fluorophenyl) wherein said aryl group is optionally substituted with 1 to 3 independently selected halogens; or

(23) phenyl;

(B) X is selected from alkyl (e.g., $-(CH_2)_q-$ or branched alkyl) or $-S(O)_2-$;

(C) Y represents

(1) a single bond (i.e., Y represents a direct bond from M^1 to M^2); or

(2) Y is selected from –C(O)-, -C(S)-, $-(CH_2)_q$ -, or $-NR^4C(O)-$; with the provisos that:

(a) when M^1 is N, then Y is not $-NR^4C(O)-$; and

(b) when Y is a bond, then M^1 and M^2 are both carbon;

(D) M^1 and M^2 are independently selected from C or N;

(E) Z is selected from: C_1-C_6 alkyl, $-SO_2-$, -C(O)- or $-C(O)NR^4-$;

(F) R^2 is selected from:

(1) a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O (i.e., N-oxide), with the remaining ring atoms being carbon;

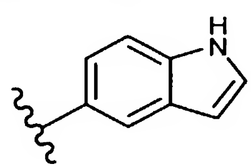
(2) a five-membered heteroaryl ring having 1 to 3 heteroatoms selected from nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; or

(3) an alkyl group, preferably a C_1 to C_4 alkyl group, more preferably methyl;

(4) an aryl group, e.g., phenyl or substituted phenyl (preferably phenyl), wherein said substituted phenyl is substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-OCF_3$, $-CF_3$, -CN, $-NO_2$, $-NHC(O)CH_3$, or $-O(CH_2)_qN(R^{10A})_2$;

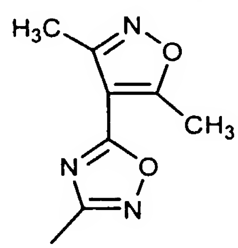
(5) $-N(R^{11A})_2$ wherein each R^{11A} is independently selected from: H, alkyl (e.g., i-propyl) or aryl (e.g., phenyl), preferably one R^{11A} is H and the other is phenyl or alkyl (e.g., i-propyl);

(6) a group of the formula:



; or

(7) a heteroarylheteroaryl group, e.g.,



;

said five membered heteroaryl ring ((F)(2) above) or six-membered heteroaryl ring ((F)(1) above) is optionally substituted with 1 to 3 substituents selected from:

(a) halogen;

(b) hydroxyl;

(c) lower alkyl;

(d) lower alkoxy;

(e) $-CF_3$;

(f) $-NR^4R^5$;

(g) phenyl;

(h) $-NO_2$;

(i) $-C(O)N(R^4)_2$ (wherein each R^4 is the same or different);

(j) $-C(O)_2R^4$; or

(k) phenyl substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-OCF_3$, $-CF_3$, -CN, $-NO_2$ or $-O(CH_2)_qN(R^{10A})_2$;

(G) R^3 is is selected from:

(1) aryl;

(2) heteroaryl;

(3) heterocycloalkyl

(4) alkyl; or

(5) cycloalkyl;

wherein said aryl or heteroaryl R^3 groups is optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen (e.g., Br, F, or Cl, preferably F or Cl);

(b) hydroxyl (i.e., -OH);

(c) lower alkoxy (e.g., C_1 to C_6 alkoxy, preferably C_1 to C_4 alkoxy, more preferably C_1 to C_2 alkoxy, most preferably methoxy);

(d) -Oaryl (i.e., aryloxy);

(e) $-SR^{22}$;

(f) $-CF_3$;

(g) $-OCF_3$;

(h) $-OCHF_2$;

(i) $-NR^4R^5$;

(j) phenyl;

(k) $-NO_2$,

(l) $-CO_2R^4$;

(m) $-CON(R^4)_2$ wherein each R^4 is the same or different;

(n) $-S(O)_2R^{22}$;

(o) $-S(O)_2N(R^{20})_2$ wherein each R^{20} is the same or different;

(p) $-N(R^{24})S(O)_2R^{22}$;

(q) -CN;

(r) $-CH_2OH$;

(s) $-OCH_2CH_2OR^{22}$; or

(t) alkyl;

(H) R^4 is selected from:

(1) hydrogen;

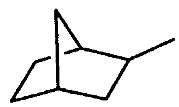
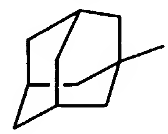
(2) C_1-C_6 alkyl;

(3) cycloalkyl;

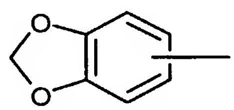
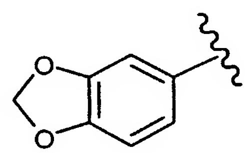
(4) cycloalkylalkyl (e.g., cyclopropyl-CH_2- or cyclohexyl-CH_2-);

(5) heterocycloalkylalky (e.g., tetrahydrofuranyl-CH_2-);

(6) bridged bicyclic cycloalkyl ring, such as, for example:

 ,  or  ;

(7) aryl having a fused heterocycloalkyl ring bound to said aryl ring, preferably the heteroatoms in said heterocycloalkyl ring are two oxygen atoms, e.g., phenyl having a heterocycloalkyl ring bound to said phenyl ring, such as

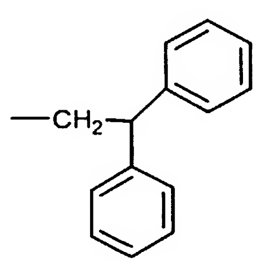
 or  ;

(8) aryl;

(9) arylalkyl;

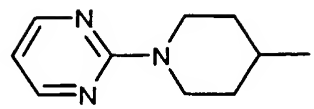
(10) alkylaryl;

(11) -$(CH_2)_dCH(R^{12A})_2$ wherein d is 1 to 3 (preferably 1), and each R^{12A} is independently selected from phenyl or substituted phenyl, said substituted phenyl being substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF_3, -CF_3, -CN, or -NO_2, e.g.,



;

(12) heterocycloalkylheteroaryl, e.g.,



; or

(13) -(C_1 to C_6)alkylene-O-R^{22} (e.g., -$C_3H_6OCH_3$);

wherein the aryl R^4 group, the aryl portion of the arylalkyl R^4 group, or the aryl portion of the alkylaryl R^4 group is optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen;

(b) hydroxyl;

(c) lower alkyl;

(d) lower alkoxy;

(e) -CF_3;

(f) -N(R^{20})(R^{24}),

(g) phenyl;

(h) -NO_2;

(i) –C(O)N(R^{20})$_2$ (wherein each R^{20} is the same or different),

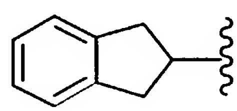
(j) -C(O)R^{22};

(i) -(CH_2)$_k$-cycloalkyl;

(j) -(CH_2)$_q$-aryl; or

(k) -(CH_2)$_m$-OR^{22};

(I) each R^{4B} is independently selected from: H, heteroaryl (e.g., pyridyl), alkyl, alkenyl (e.g., allyl), a group of the formula



,

arylalkyl (e.g., benzyl), or arylalkyl wherein the aryl moiety is substitued with 1-3 substituents independently selected from: halogen (e.g. –CH_2-p-Clphenyl); preferably one R^{4B} is H;

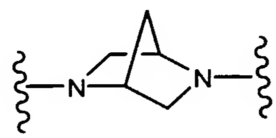
(J) R^5 is selected from: hydrogen, C_1-C_6 alkyl, -C(O)R^{20} (e.g., -C(O)alkyl, such as –C(O)CH_3), -C(O)$_2R^{20}$, –C(O)N(R^{20})$_2$ (wherein each R^{20} is the same or different);

(K) each R^{10A} is independently selected from H or C_1 to C_6 alkyl (e.g., methyl), or each R^{10A}, taken together with the nitrogen atom to which they are bound, forms a 4 to 7 membered heterocycloalkyl ring;

(L) R^{12} is

(1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R^{12} is hydroxy or fluoro then R^{12} is not bound to a carbon adjacent to a nitrogen; or

(2) R^{12} forms an alkyl bridge from one ring carbon to another ring carbon, an example of such a bridged ring system is:

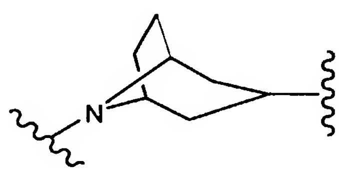


;

(M) R^{13} is

(1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R^{13} is hydroxy or fluoro then R^{13} is not bound to a carbon adjacent to a nitrogen; or

(2) R^{13} forms an alkyl bridge from one ring carbon to another ring carbon, an example of such a bridged ring system is:



(N) R^{20} is selected from hydrogen, alkyl, or aryl, wherein said aryl group is optionally substituted with from 1 to 3 groups independently selected from: halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy; or when two R^{20} groups are present, said two R^{20} groups taken together with the nitrogen to which they are bound form a five or six membered heterocyclic ring;

(O) R^{22} is selected from: heterocycloalkyl (e.g., morpholinyl or pyrrolidinyl), alkyl or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;

(P) R^{24} is selected from: hydrogen, alkyl, $-SO_2R^{22}$, or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;

(Q) a is 0 to 2;

(R) b is 0 to 2;

(S) k is 1 to 5;

(T) m is 2 to 5;

(U) n is 1, 2 or 3 with the proviso that when M^1 is N, then n is not 1;

(V) p is 1, 2 or 3 with the proviso that when M^2 is N, then p is not 1;

(W) q is 1 to 5; and

(X) r is 1, 2, or 3 with the proviso that when r is 2 or 3, then M^2 is C and p is 1.

This invention also provides a pharmaceutical composition comprising an effective amount of compound of Formula I, and a pharmaceutically acceptable carrier.

This invention further provides a method of treating: allergy, allergy-induced airway (e.g., upper airway) responses, congestion (e.g., nasal congestion), hypotension, cardiovascular disease, hypotension, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders (e.g., hypersomnia, somnolence, and narcolepsy), disturbances of the central nervous system, attention deficit hyperactivity disorder ADHD), hypo and hyperactivity of the central nervous system (for example, agitation and depression), and/or other CNS disorders (such as Alzheimer's, schizophrenia, and migraine) comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a method of treating: allergy comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a method of treating: allergy-induced airway (e.g., upper airway) responses comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a method of treating: congestion (e.g., nasal congestion) comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a pharmaceutical composition comprising an effective amount of a compound of Formula I, and an effective amount of a H_1 receptor antagonist in combination with a pharmaceutically acceptable carrier.

This invention further provides a method of treating: allergy, allergy-induced airway (e.g., upper airway) responses, and congestion (e.g., nasal congestion)

comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H_1 receptor antagonist.

This invention further provides a method of treating: allergy comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H_1 receptor antagonist.

This invention further provides a method of treating: allergy-induced airway (e.g., upper airway) responses comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H_1 receptor antagonist.

This invention further provides a method of treating: congestion (e.g., nasal congestion) comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H_1 receptor antagonist.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms have the following meanings, unless indicated otherwise:

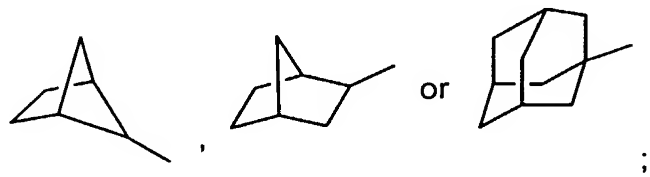
alkyl-(including the alkyl portions of alkylamino, alkylaryl, arylalkyl, alkoxy and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

alkylaryl-represents an alkyl group, as defined above, bound to an aryl group, as defined below, wherein said aryl group is bound to the compound;

aryl (including the aryl portion of alkylaryl and arylalkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl or naphthyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with one or more (e.g., 1 to 3) substituents independently selected from: halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, amino, alkylamino, dialkylamino, $-COOR^{20}$ or $-NO_2$;

arylalkyl-represents an aryl group, as defined above, bound to an alkyl group, as defined above, wherein said alkyl group is bound to the compound;

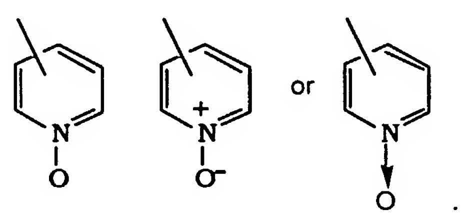
bridged bicyclic cycloalkyl rings-represents a cycloalkyl ring, as defined below, having an alkyl (as defined above) bridge from one ring carbon to another ring carbon thereby forming a bicyclic cycloalkyl ring, e.g.,



cycloalkyl-represents saturated carbocyclic rings of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

halo (halogen)-represents fluoro, chloro, bromo and iodo; and

heteroaryl-represents cyclic groups, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms; examples include but are not limited to isothiazolyl, isoxazolyl, oxazolyl, furazanyl, triazolyl, thiazolyl, thienyl, furanyl (furyl), pyrrolyl, pyrazolyl, pyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyridyl (e.g., 2-, 3-, or 4-pyridyl), pyridyl N-oxide (e.g., 2-, 3-, or 4-pyridyl N-oxide), triazinyl, pteridinyl, indolyl (benzopyrrolyl), pyridopyrazinyl, isoqinolinyl, quinolinyl, naphthyridinyl, wherein said pyridyl N-oxide can be represented as:



heterocycloalkyl-represents a saturated, carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S-, -SO-, $-SO_2$ or $-NR^{40}$- wherein R^{40} represents H, C_1 to C_6 alkyl, arylalkyl, $-C(O)R^{20}$, $-C(O)OR^{20}$, or -$C(O)N(R^{20})_2$ (wherein each R^{20} is independently selected); examples include but are not limited to 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, 1,3-dioxolanyl, 1,3,5-trithianyl, pentamethylene sulfide, perhydroisoquinolinyl, decahydroquinolinyl, trimethylene oxide, azetidinyl, 1-azacycloheptanyl, 1,3-dithianyl, 1,3,5-trioxanyl,

morpholinyl, thiomorpholinyl, 1,4-thioxanyl, and 1,3,5-hexahydrotriazinyl, thiazolidinyl, tetrahydropyranyl;

heterocycloalkylheteroaryl-represents a heteroaryl group as defined above bound to a heterocycloalkyl as defined above;

lower alkyl-represents an alkyl group, as defined above, that comprises 1 to 6 carbon atoms, preferably 1-4 carbon atoms;

lower alkoxy-represents an alkoxy group whose alkyl moiety comprises 1 to 6 carbon atoms, preferably 1-4 carbon atoms;

Ac-represents acetyl (i.e.,$CH_3C(O)$-);

t-BOC-represents t-butyloxycarbonyl;

Ci/mmol-represents curie/mmol (a measure of specific activity);

DCC-represents dicyclohexylcarbodiimide;

DEC-represents 2-diethylaminoethyl chloride hydrochloride;

DIC-represenets diisopropylcarbodiimide;

DMF-represents dimethylformamide;

DMSO-represents dimethylsulfoxide;

EtOAc-represents ethyl acetate;

EtOH-represents ethanol;

FMOC-represents 9-fluorenylmethoxycarbonyl;

HOBT-represents 1-hydroxybenzotriazole;

Ki-represents inhibition constant for substrate/receptor complex;

LiOH-represents lithium hydroxide;

Me-represents methyl;

MeOH-represents methanol;

nM-represents nanomolar;

PyBOP-represents benzotriazole-1-yl-oxy-trispyrrolidino-phosphonium hexaflurophosphate;

TFA-represents trifluoroacetic acid;

THF-represents tetrahydrofuran;

Also, as used herein, “upper airway” usually means the upper respiratory system--i.e., the nose, throat, and associated structures.

Also, as used herein, “effective amount” generally means a therapeutically efffective amount.

Lines drawn into the rings indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers, diastereoisomers and geometric) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

The compounds of this invention are ligands for the histamine H_3 receptor. The compounds of this invention can also be described as antagonists of the H_3 receptor, or as H_3 antagonists.

The compounds of the invention are basic and form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their corresponding salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their corresponding free base forms for purposes of this invention.

The compounds of Formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

The compounds of this invention can be combined with an H_1 receptor antagonist (i.e., the compounds of this invention can be combined with an H_1 receptor antagonist in a pharmaceutical composition, or the compounds of this invention can be administered with H_1 receptor antagonist).

Numerous chemical substances are known to have histamine H_1 receptor antagonist activity and can therefore be used in the methods of this invention. Many H_1 receptor antagonist useful in the methods of this invention can be classified as ethanolamines, ethylenediamines, alkylamines, phenothiazines or piperidines.

Representative H_1 receptor antagonists include, without limitation: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine (also known as SCH-34117), diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine. Other compounds can readily be evaluated to determine activity at H_1 receptors by known methods, including specific blockade of the contractile response to histamine of isolated guinea pig ileum. See for example, WO98/06394 published February 19, 1998.

Those skilled in the art will appreciate that the H_1 receptor antagonist is used at its known therapeutically effective dose, or the H_1 receptor antagonist is used at its normally prescribed dosage.

Preferably, said H_1 receptor antagonist is selected from: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.

More preferably, said H_1 receptor antagonist is selected from: astemizole, azatadine, azelastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, carebastine, descarboethoxyloratadine, diphenhydramine, doxylamine, ebastine, fexofenadine, loratadine, levocabastine, mizolastine, norastemizole, or terfenadine.

Most preferably, said H_1 receptor antagonist is selected from: azatadine, brompheniramine, cetirizine, chlorpheniramine, carebastine, descarboethoxy-loratadine (also known as SCH-34117), diphenhydramine, ebastine, fexofenadine, loratadine, or norastemizole.

Even more preferably, said H_1 antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine or cetirizine. Still even more preferably, said H_1 antagonist is loratadine or descarboethoxyloratadine.

In one preferred embodiment, said H_1 receptor antagonist is loratadine.

In another preferred embodiment, said H_1 receptor antagonist is descarboethoxyloratadine.

In still another preferred embodiment, said H_1 receptor antagonist is fexofenadine.

In yet another preferred embodiment, said H_1 receptor antagonist is cetirizine.

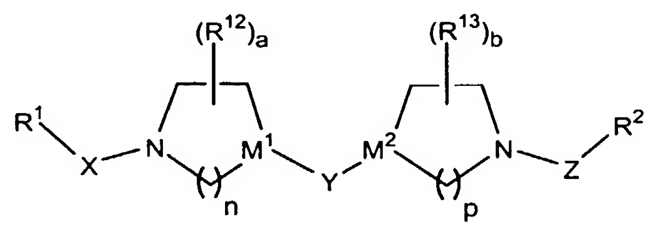
Preferably, in the above methods, allergy-induced airway responses are treated.

Also, preferably, in the above methods, allergy is treated.

Also, preferably, in the above methods, nasal congestion is treated.

In the methods of this invention wherein a combination of an H_3 antagonist of this invention (compound of Formula I) is administered with a H_1 antagonist, the antagonists can be administered simultaneously, consecutively (one after the other within a relatively short period of time), or sequentially (first one and then the other over a period of time). In general, when the antagonists are administered consecutively or sequentially, the H_3 antagonist of this invention (compound of Formula I) is administered first.

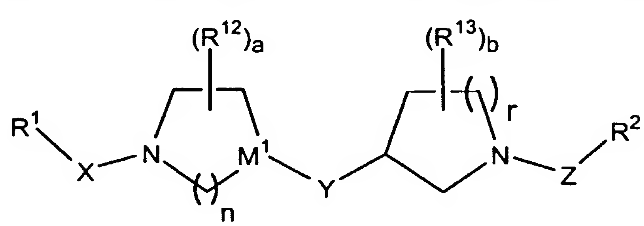
Compounds of Formula I include compounds of the formula:



(V)

wherein R^1, X, n, M^1, R^{12}, a, Y, M^2, R^{13}, b, p, Z and R^2 are as defined for Formula I.

Compounds of Formula I also include compounds of the formula:



(VI)

wherein R^1, X, n, M^1, R^{12}, a, Y, R^{13}, b, r, Z and R^2 are as defined for Formula I.

R^1 is preferably selected from:

(1) substituted aryl, more preferably substituted phenyl;

(2) substituted heteroaryl, more preferably substituted isoxazolyl; or

(3) formula IVA wherein each R^3 is independently selected, more preferably each R^3 is alkyl, most preferably each R^3 is C_1 to C_4 alkyl, even more preferably each R^3 is the same moiety, and still more preferably each R^3 is methyl.

Preferably, when R^1 is a substituted phenyl group, the phenyl group has 1 to 3 substituents and the substituents are independently selected from:

(1) $-C(O)N(R^4)_2$, preferably each R^4 is independently selected, more preferably each R^4 is independently selected from H or arylalkyl (e.g., $-CH_2CH_2$phenyl), most preferably one R^4 is H and the other is arylalkyl, even more preferably one R^4 is H and the other R^4 is $-CH_2CH_2$phenyl;

(2) halo, more preferably 1 to 3 halos independently selected from Br, Cl and F;

(3) $-S(O)_2R^{22}$, more preferably R^{22} is heterocycloalkyl, most preferably R^{22} is morpholinyl or pyrrolidinyl;

(4) $-OCF_3$;

(5) $-OCHF_2$; or

(6) $-S(O)_2N(R^{20})_2$, more preferably each R^{20} is independently selected from alkyl or substituted phenyl, most preferably C_1 to C_4 alkyl or halo substituted phenyl, even more preferably methyl or chlorophenyl; still more preferably each R^{20} is methyl or one R^{20} is methyl and the other R^{20} is chlorophenyl.

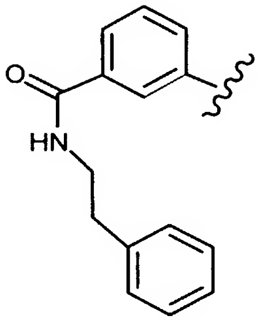
Preferably, when R^1 is a substituted isoxazolyl group the isoxazolyl group has 1 or 2 substituents independently selected from:

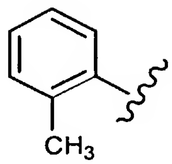
(1) alkyl, more preferably C_1 to C_4 alkyl, most preferably methyl; or

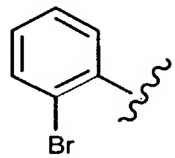
(2) substituted phenyl, more preferably halo substituted phenyl (1 to 3 halo groups, preferably one halo group), most preferably chloro substituted phenyl (e.g., chlorophenyl).

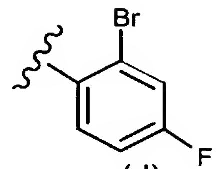
More preferably the isoxazolyl is substituted with two alkyl groups (most preferably two methyl groups), or one halophenyl group (most preferably chlorophenyl).

Examples of R^1 groups include but are not limited to:


(a) ,


(b) ,


(c) ,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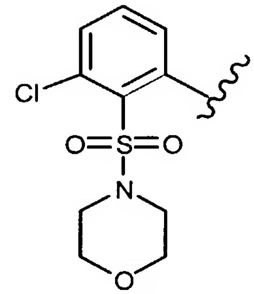
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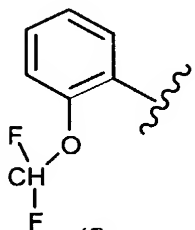
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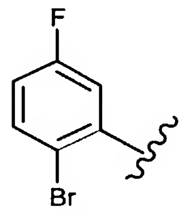
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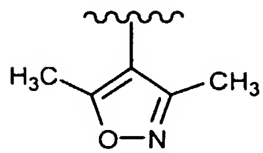
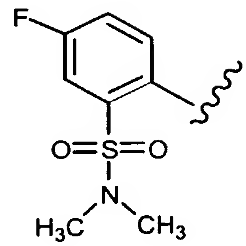
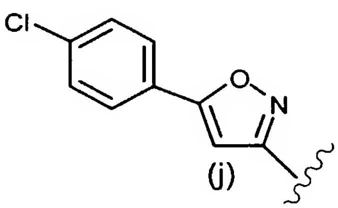

(h) ,


(i) ,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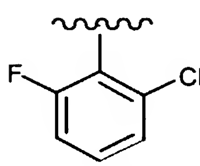
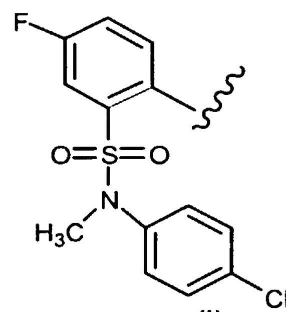
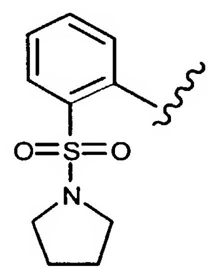
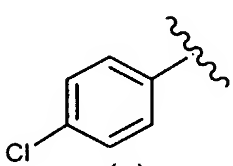
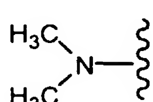
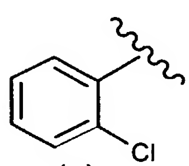

(k) ,

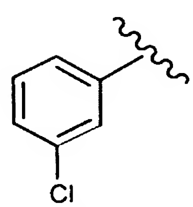

(l) ,

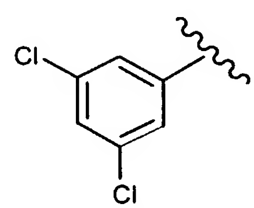

(m) ,

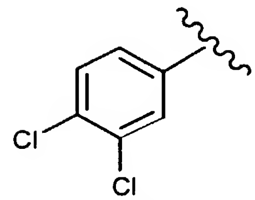

(n) ,


(o) ,


(p) ,


(q) ,


(r) , or



(s)

Preferably X is selected from $-CH_2-$ (i.e., q is preferably 1) or $-SO_2-$. More preferably X is $-CH_2-$.

Preferably n is 2.

Preferably M^1 is N.

Preferably Y is $-C(O)-$.

Preferably M^2 is C.

Preferably p is 2.

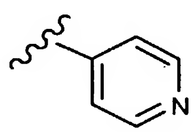
Preferably r is 1.

Preferably Z is a C_1 to C_6 alkyl group. More preferably Z is

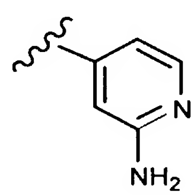
$$-CH_2- \quad \text{or} \quad -\overset{\displaystyle CH_3}{\overset{|}{C}}H- \ .$$

Most preferably Z is $-CH_2-$.

Preferably R^2 is a six membered heteroaryl ring or a substituted six membered heteroaryl ring, and more preferably the heteroaryl ring contains one nitrogen atom. Preferably the substituted heteroaryl ring is substituted with one $-NR^4R^5$, and more preferably the substituent is $-NH_2$. Most preferably R^2 is selected from

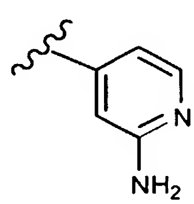


or



.

Even more preferably R^2 is



.

Preferably a is 0 and therefore there is no R^{12} group present.

Preferably b is 0 or 1, more preferably 0. When b is 1 R^{13} is preferably $-OH$. More preferably, when b is 1, R^{13} is $-OH$ bound to the M^2 substituent and M^2 is C.

Representative compounds of this invention include, but are not limited to: Compounds 18 (Example 1), 25 (Example 2), 26 (Example 3), 31 (Example 4), 33 (Example 5), 37 (Example 6), 41 (Example 7), 45 (Example 8), 49 (Example 9), 51 (Example 10), 52 (Example 11), 57 (Example 12), 58 to 67, 73 to 84, 89 to 157, 159 to 168, 212 to 269, 271 to 272, 276 to 282, 284, 285, 287 to 300, 306, 309 to 319, 321 to 336, 338 to 340, 342 to 349, 351 to 361, 363 to 371, 374 to 377, 380 to 383, 387 to 390, 392 to 406, and 408 to 410.

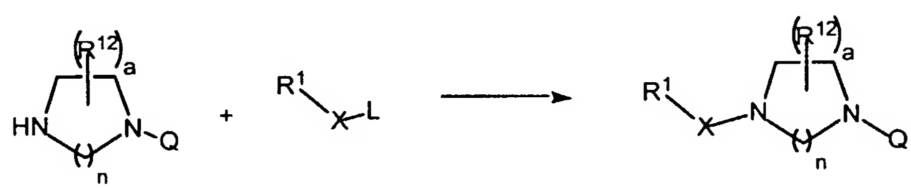
Preferred compounds are Compounds 93, 276, 306, 317, 331, 332, 333, 336, 366, 343, 366, 367, 374, and 376

More preferred compounds are Compounds 306, 332, 333, 336, 366, 374, and 376.

Structures for the above compounds are given below.

The following processes may be employed to produce compounds of the invention.

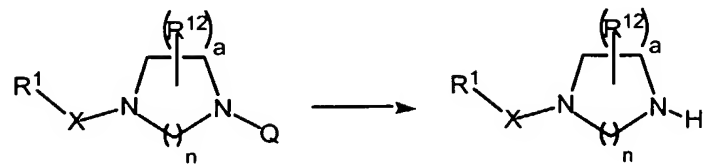
Step 1



1 2 3

In Step 1, compound **1**, in which Q is a protecting group such as a carbamate, amide, or a substituted benzylic group, is allowed to react with compound **2**, in which L is a leaving group such as a halogen atom, in a suitable solvent such as THF, DMSO or DMF in the presence of a base such as a tertiary amine or an inorganic base such as Na_2CO_3 at a temperature sufficient to achieve a reasonable reaction rate. R^{12}, M^1, n, a, R^1, and X are as defined above. Alternatively, in the case when X is $-(CH_2)_q-$, L can equal an aldehyde group, CHO and X is $-(CH_2)_{q-1}-$. In that case, compounds **1** and **2** are combined in a solvent such as trifluoroethanol in the presence of sieves. A reducing agent, such as $NaBH(OAc)_3$ or $NaCNBH_3$ is added and the reaction stirred at a temperature suitable to complete the reaction.

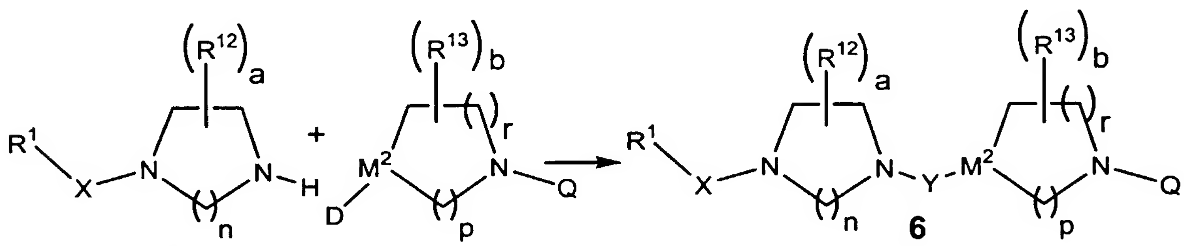
Step 2



3 4

In Step 2, the protecting group Q is removed. When said protecting group is a carbamate such as t-BOC, dilute acid is used. In the case of a benzyl group, catalytic hydrogenation is used.

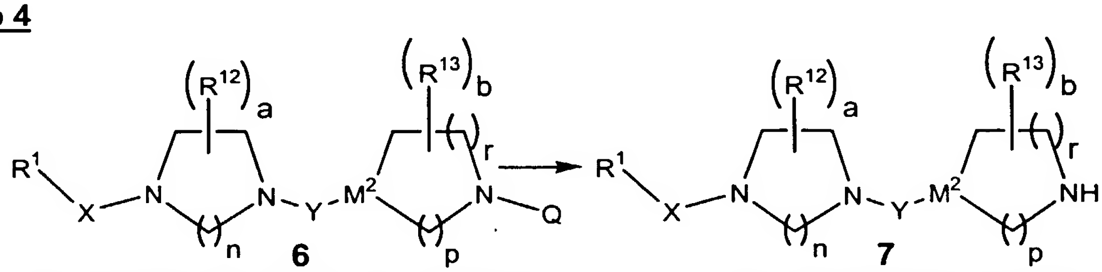
Step 3



4 5 6

When Y is C=O, amine **4** can be coupled to acid **5** (D is CO_2H, M^2 is carbon) using a number of methods well known in the art such as DCC or PyBOP. Alternatively, the acid **5** can be activated by conversion to the acid chloride or mixed anhydride and then reacted with the amine **4** to give **6**. Suitable protecting groups for **5** include t-Boc or the like. Alternatively, when Y is $-CH_2$- and M^2 is carbon, D can be $-CH_2$-L (where L is a halogen) and the reaction can be performed as in Step 1.

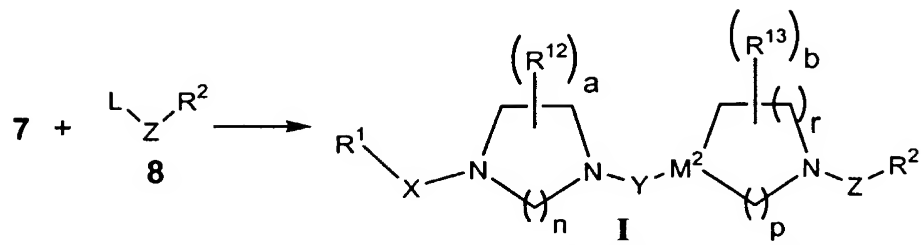
Step 4



6 7

Compound **6** in which the protecting group is a t-Boc can be deprotected under acidic conditions such as HCl in dioxane or TFA in CH_2Cl_2 to give the amine **7**.

Step 5

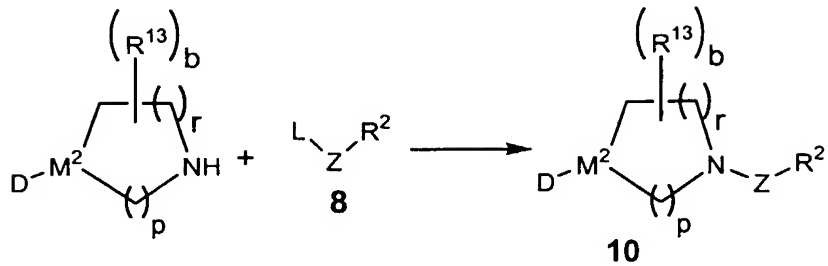


The amine **7** can be alkylated by reaction with the electrophile **8**. In one case, L represents a carbonyl group and Z is a branched or straight chain alkyl group. Compounds **7** and **8** are combined in a solvent such as CH_2Cl_2 in the presence of sieves. After a suitable amount of time, a reducing agent such as $NaBH(OAc)_3$ is added to give the product **I**. Alternatively, when L is a halogen atom such as Cl or Br, and Z is a branched or straight chain alkyl group or $-SO_2-$ **7** and **8** are combined in a solvent such as DMF in the presence of a tertiary amine base to give the product **I**.

<u>**Alternative Synthesis**</u>

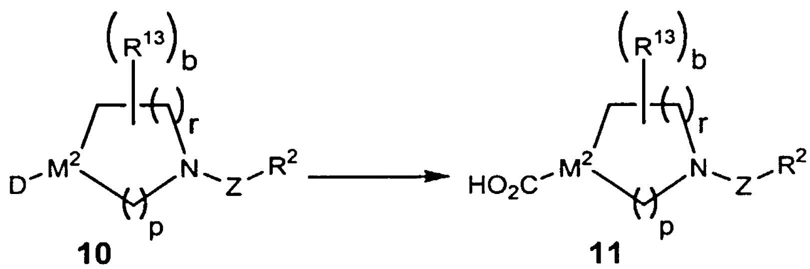
An alternative approach to the synthesis of compounds of Formula I is given below.

Step 1



In the same manner as Step 5, compounds **8** and **9** can be converted to **10**. In the case when M^2 is carbon, D is CO_2alkyl and when M^2 is nitrogen, D is a protecting group such as the BOC group.

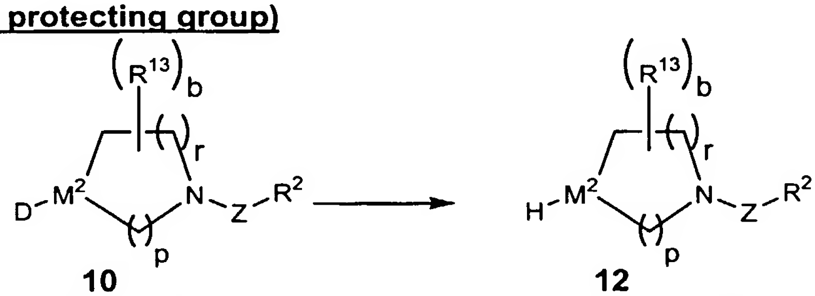
Step 2



Compound **10** (D is CO_2alkyl) is saponified in a mixed solvent such as EtOH or MeOH and water, or THF, water, and MeOH using an alkali metal base such as LiOH or NaOH at a temperature of from 50 to 100°C to give **11**.

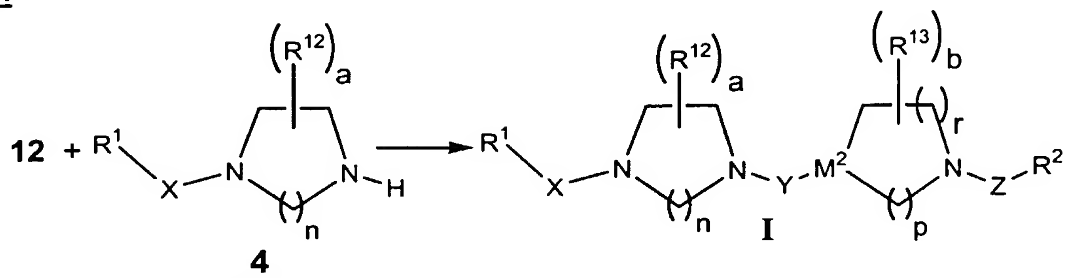
Compound **11** can be combined with compound **4** as described in Step 3.

Step 3 (D is a protecting group)



Compound **10**, in which D is a protecting group such as t-Boc and M^2 is nitrogen, can be deprotected under acidic conditions such as HCl in dioxane or TFA in CH_2Cl_2 to give the amine **12**.

Step 4



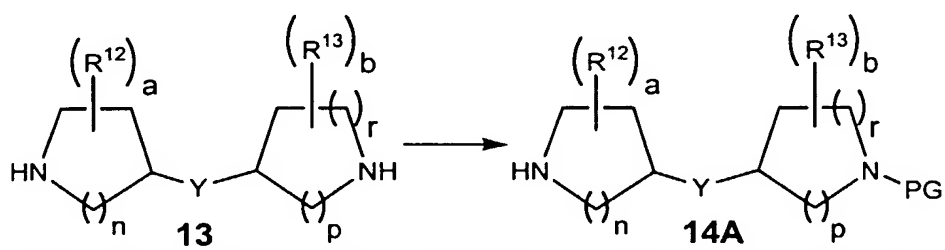
Compound **12** can be coupled with compound **4** using a reagent such as carbonyl diimidazole or the like in a solvent such as THF, ether or the like at a temperature from 0 to 60°C to give compound **I** (Y is C=O, M^1 and M^2 are nitrogen).

Step 5

Compound **I** (Y is C=O) can be converted to compound **I** (Y is C=S) by treatment of **I** with a reagent such as Lawesson's reagent in a solvent such as toluene at a temperature from 20 to 100°C.

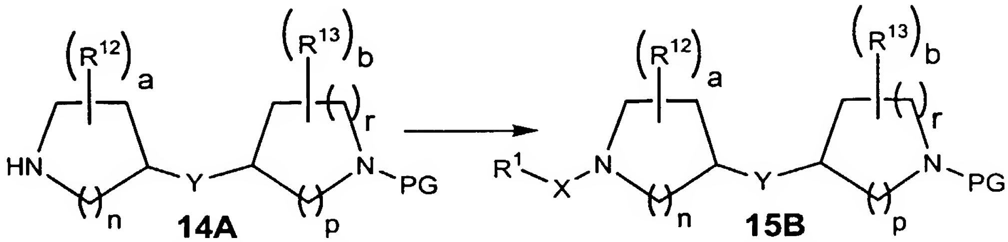
Synthesis (M^1 and M^2 are carbon)

Step 1



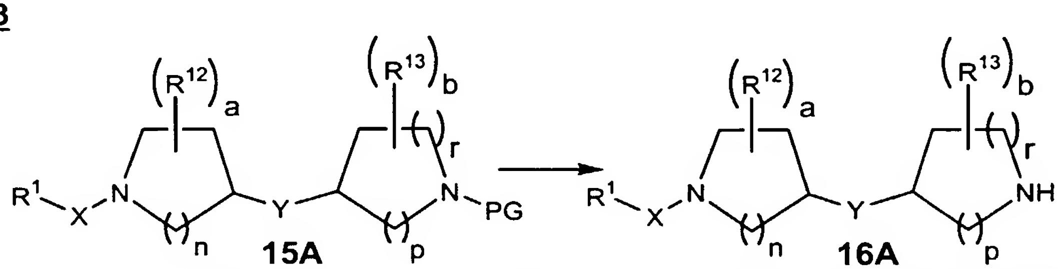
A solution of an excess of **13** in a solvent such as THF, CH_2Cl_2 or the like is treated with a reagent such as BOC_2O or an acid chloride or anhydride at a temperature of from –20° C to +30° C to produce **14A** in which PG is a BOC group, or an amide. Alternatively, a solution of an excess of **13** in a solvent such as THF, CH_2Cl_2 or the like is treated with a substituted or unsubstituted benzyl bromide in the presence of a base such as triethylamine to give **14A** in which PG is a substituted benzyl group.

Step 2



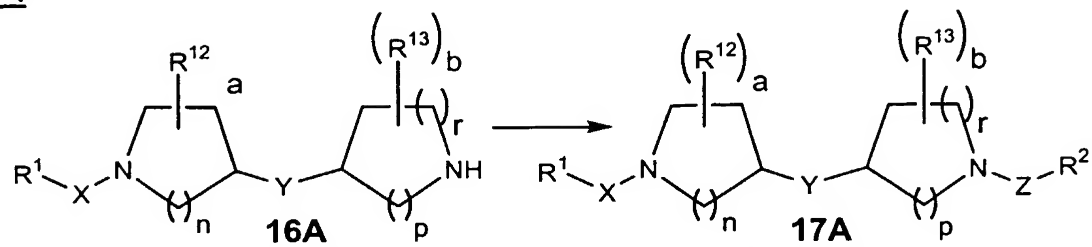
In Step 2, compound **14A**, in which PG is a protecting group such as a carbamate, amide, or a substituted benzylic group, is allowed to react with compound **2**, in which L is a leaving group such as a halogen atom, in a suitable solvent such as THF, DMSO or DMF in the presence of a base such as a tertiary amine or an inorganic base such as Na_2CO_3 at a temperature sufficient to achieve a reasonable reaction rate to give compound **15A**. R^{12}, R^{13}, M^1, n, p, a, b, r, R^1, and X are as defined for formula I. Alternatively, in the case when X is $-(CH_2)_q-$, L can equal an aldehyde group, CHO, and X is $-(CH_2)_{q-1}-$. In that case, compounds **14A** and **2** are combined in a solvent such as trifluoroethanol in the presence of sieves and stirred for a suitable time. A reducing agent, such as $NaBH(OAc)_3$ or $NaCNBH_3$ is added and the mixture stirred at a temperature suitable to complete the reaction.

Step 3



Compound **15A** in which the protecting group is t-Boc can be deprotected under acidic conditions such as HCl in dioxane or TFA in CH_2Cl_2 to give the amine **16A**. Alternatively, when PG is a benzyl group, it can be removed by catalytic hydrogenation using a catalyst such as Pd/C.

Step 4

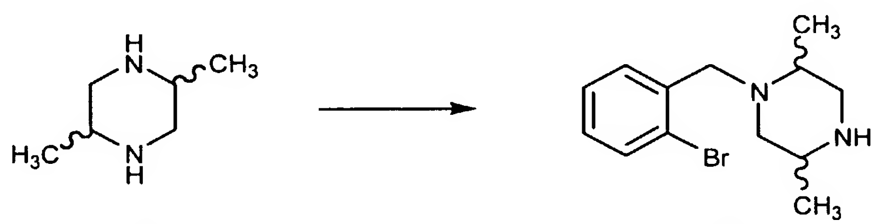


The amine **16A** can be alkylated by reaction with the electrophile **8**. In one case, L represents a carbonyl group and Z is a branched or straight chain alkyl group. Compounds **16A** and **8** are combined in a solvent such as CH_2Cl_2 in the presence of sieves. After a suitable amount of time, a reducing agent such as $NaBH(OAc)_3$ is added to give the product **17A**. Alternatively, when L is a halogen atom such as Cl or Br, and Z is a branched or straight chain alkyl group or $-SO_2-$ **16A** and **8** are combined in a solvent such as DMF in the presence of a tertiary amine base to give the product **17A**.

Compounds useful in this invention are exemplified by the following examples which should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

Example 1

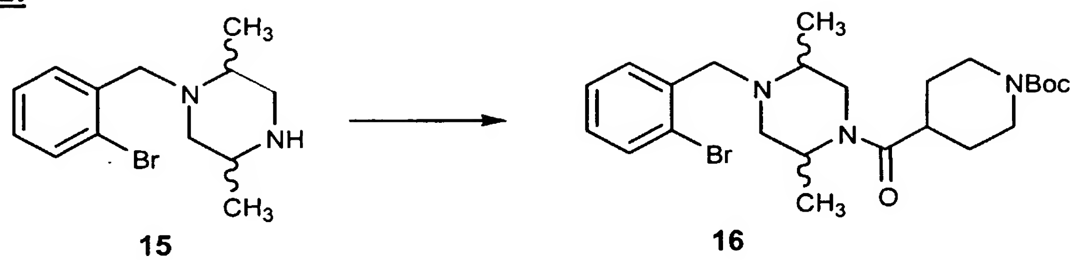
Step 1:



14 **15**

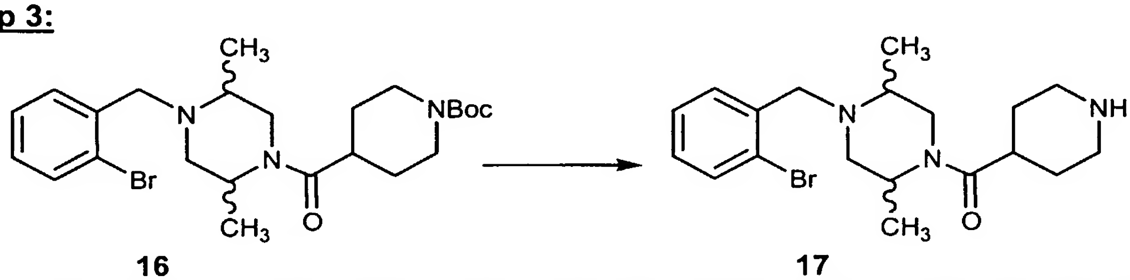
Compound **14** (5 g, 43.8 mmol) and 2-bromobenzaldehyde (4.1 g, 22.2 mmol) were combined in CH_2Cl_2 (130 mL) and stirred for 2 h. $Na(OAc)_3BH$ (6.4 g, 30.2 mmol) was added and the mixture stirred overnight at room temperature. The reaction was then washed with saturated $NaHCO_3$ and brine and dried. Filtration and concentration gave a residue which was purified by flash column chromatography (5% to 10% $MeOH/NH_3$ in CH_2Cl_2) to give **15** (3.44 g, 55%) Mass spectrum = 453 (M+H).

Step 2:



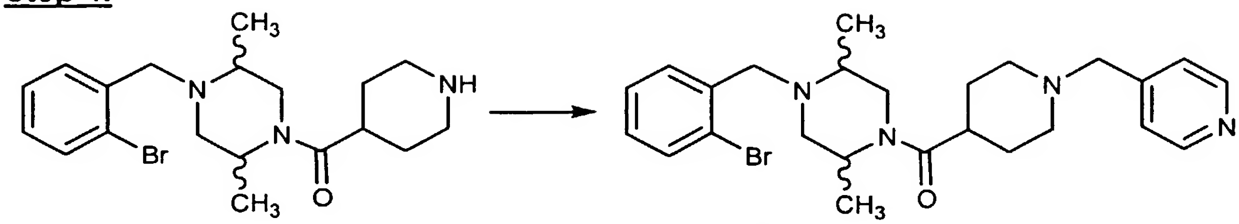
A solution of **15** (2 g, 7.06 mmol), N-Boc isonipecotic acid (1.47 g, 6.42 mmol) and PyBOP (3.34 g, 6.42 mmol) in CH_2Cl_2 (20 mL) was cooled to 0°C and diisopropyl ethyl amine (2.49 g, 19.3 mmol) was added. After 1 minute, the cooling bath was removed and the reaction stirred at room temperature for 48 hours. The reaction was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated and the residue was purified by flash column chromatography (30% to 50 % ethyl acetate in hexane) to give **16** (3 g, 60%).

Step 3:



A solution of **16** (3 g, 6.07 mmol) in CH_2Cl_2 (100 mL) at 0° C was treated with 4 N HCl (8 mL) and the reaction stirred at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in water and the pH adjusted to 8 by addition of aqueous NaOH. The water was removed in vacuo and the residue dissolved in MeOH, filtered and concentrated to give **17** as a white solid (3 g, >100%) which was used as is. Mass spectrum: 394 (M+H).

Step 4:

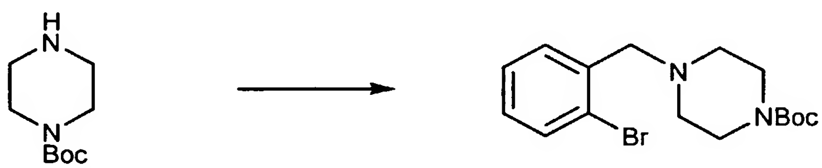


17 **18**

In a manner similar to that described in Example 1, Step 1, **17** (0.95 g, 2.4 mmol) and pyridine-4-carboxaldehyde (0.22 g, 2.02 mmol) was converted to **18** (0.57 g, 58%). Mass spectrum: 485 (M+H).

Example 2

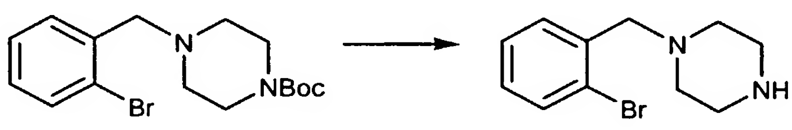
Step 1:



19 **20**

In a manner similar to that described in Example 1, Step 1, **19** (5 g, 26 mmol) and 2-bromobenzaldehyde (4.1 g, 21.7 mmol) was converted to **20** (6.2 g, 80%).

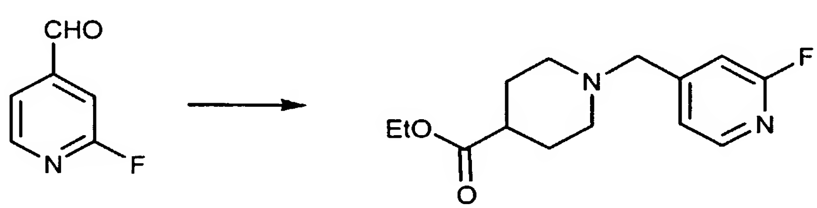
Step 2:



20 **21**

In a manner similar to that described in Example 1, Step 3, **20** (6.2 g, 17.5 mmol) was converted to **21** (5.5 g, 100%).

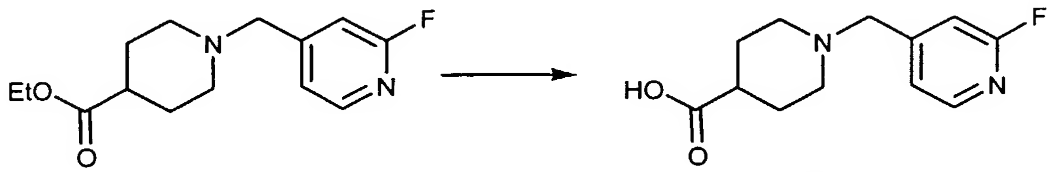
Step 3



22 **23**

In a manner similar to that described in Example 1, Step 1, **22** (0.45 g, 3.6 mmol) and ethyl isonipecotate (0.7, 4.4 mmol) were converted to **23** (0.45 g, 64%).

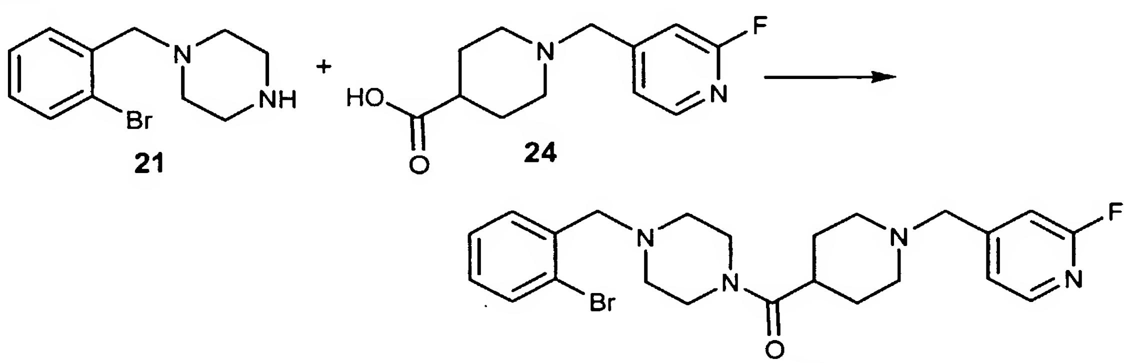
Step 4:



23 **24**

A solution of **23** (0.45 g, 1.69 mmol) in MeOH (10 mL) was treated with 1 N KOH (5 mL) and the mixture was heated to 60° C overnight. The reaction was cooled and concentrated. The residue was dissolved in water and extracted with ethyl acetate. The pH of the aqueous phase was adjusted to 6-7 by addition of 1N HCl. The water was removed in vacuo and the residue taken up in MeOH, filtered and concentrated to give **24** which was used in the next step as is.

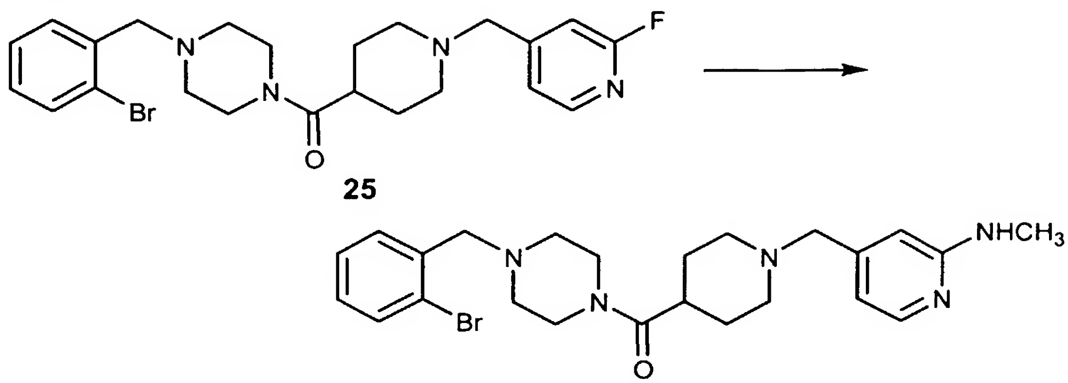
Step 5:



21 **24** **25**

In a manner similar to that described in Example 1, Step 2, **21** (0.35 g, 1.39 mmol) and **24** (0.3 g, 1.26 mmol) was converted to **25** (0.50 g, 66%). Mass spectrum: 475 (M+H).

Example 3

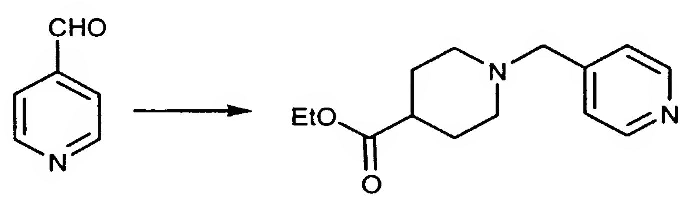


25 **26**

To a solution of **25** (0.11 g, 0.23 mmol) in 2-propanol (6 mL) in a pressure vessel was added triethylamine (7 mL) and methylamine hydrochloride (3 g, 44.4 mmol) and the reaction heated to 95°C for 6 days. The reaction was cooled and the solvent removed in vacuo. The residue was dissolved in ethyl acetate and washed with half saturated $NaHCO_3$. The organic layer was dried and concentrated, and the residue purified on a flash column (20% MeOH in ethyl acetate) to give **26** (40 mg, 36%). Mass spectrum: 486 (M+H).

Example 4

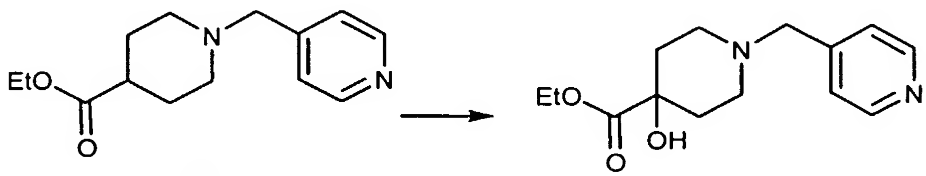
Step 1:



27 **28**

In a manner similar to that described in Example 1, Step 1, **27** (2 g, 18.3 mmol) and ethyl isonipecotate (3.5, 22 mmol) were converted to **28** (4.5 g, 99%).

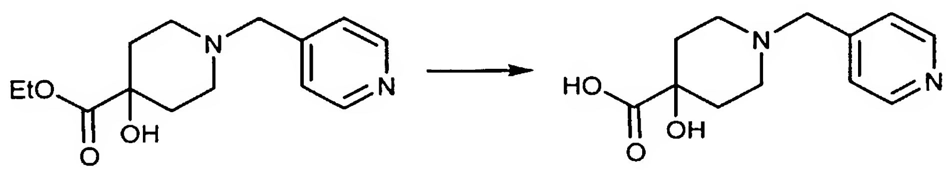
Step 2:



28 **29**

A solution of n-BuLi (3 mL of a 1.6 M solution in hexane, 4.8 mmol) in THF (25 mL) was treated at – 25° C with $(i\text{-}Pr)_2NH$ (0.49 g, 4.8 mmol). The reaction was stirred for 1 h at 0°C and then cooled to – 70° C. Compound **28** (1.0 g, 4 mmol) in THF (3 mL) was added dropwise and the reaction stirred at – 70°C for 2 h and – 50° C for 2 h. The reaction was recooled to – 70° C and (1S)-(+)-(10-camphorsulfonyl)oxaziridine (1.04 g, 4.52 mmol) in THF (10 mL) was added. The reaction was stirred at – 70° C for 2 h and slowly warmed to room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried and concentrated, and the residue purified by column chromatography (4% MeOH in ethyl acetate) to give **29** (0.75 g, 71%).

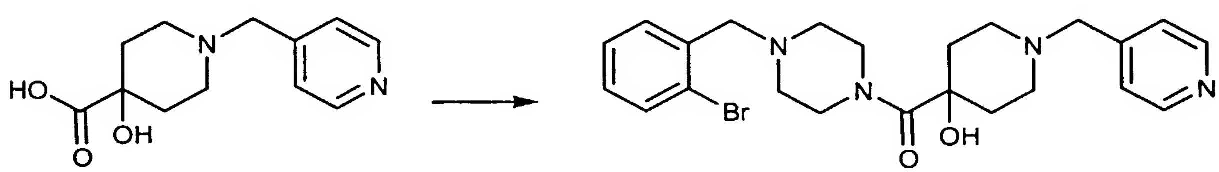
__Step 3:__



29 **30**

In a manner similar to that described in Example 2, Step 4, **29** (0.35 g, 1.32 mmol) was converted to **30** (0.32 g, 99%).

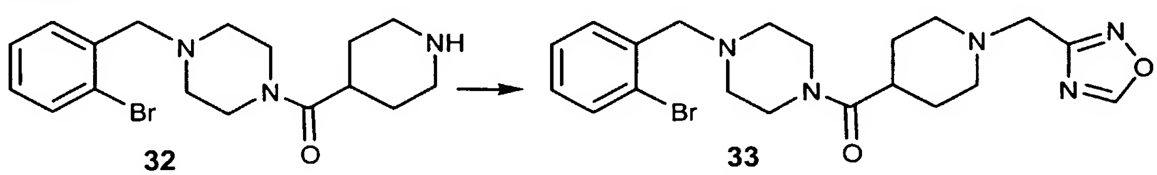
__Step 4:__



30 **31**

In a manner similar to that described in Example 1, Step 2, **30** (0.2 g, 0.85 mmol) was converted to **31** (0.10 g, 25%). Mass spectrum: 473 (M+H).

__Example 5__

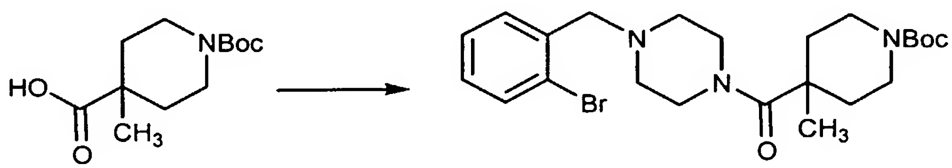


32 **33**

To a solution of **32** (0.52 g, 1.43 mmol; synthesized in the same manner as compound **17**) and 3-chloromethyloxadiazole (0.25g, 2.11 mmol) in toluene (10 mL) was added triethylamine (0.6 mL) and the reaction was heated to 75° C overnight. The reaction was cooled, diluted with ethyl acetate and washed with saturated $NaHCO_3$. The organic layer was dried and concentrated and the residue purified by flash column chromatography (10% MeOH in ethyl acetate) to give **33** (0.2 g, 31%) Mass spectrum: 448 (M+H).

Example 6

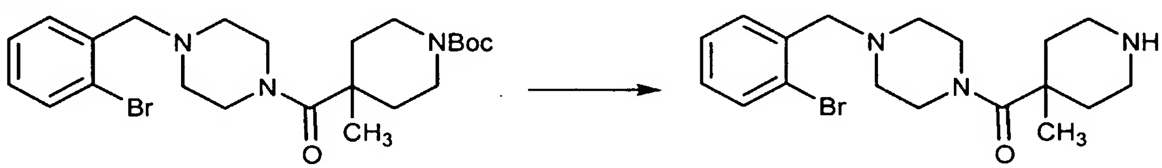
Step 1



34 **35**

In a manner similar to that described in Example 1, Step 2, compound **34** (1.2 g, 4.93 mmol) was coupled with compound **21** (1.4 g, 5.43 mmol) to give compound **35** (1.7 g, 74%).

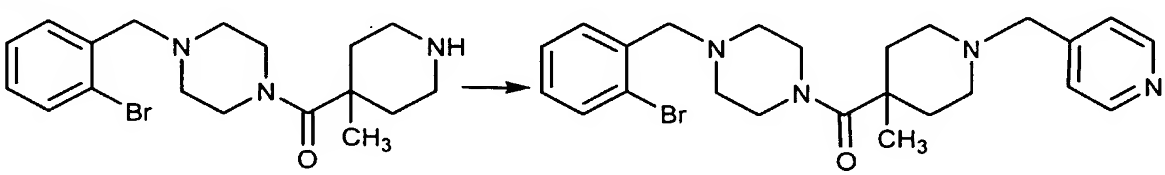
Step 2



35 **36**

In a manner similar to that described in Example 1, Step 3, compound **35** (1.7 g, 3.54 mmol) was converted to **36** (1.3 g, 97%).

Step 3

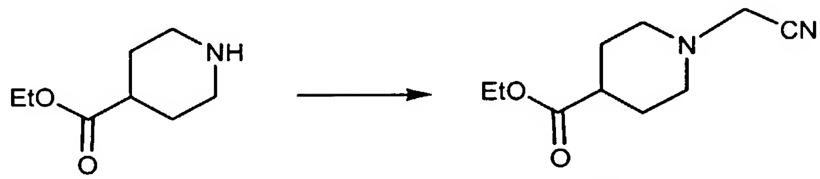


36 **37**

In a manner similar to that described in Example 1, Step 1, compound **36** (0.41 g, 1.08 mmol) was converted to **37** (0.2 g, 45%). Mass Spectrum : 471 (M+H).

Example 7

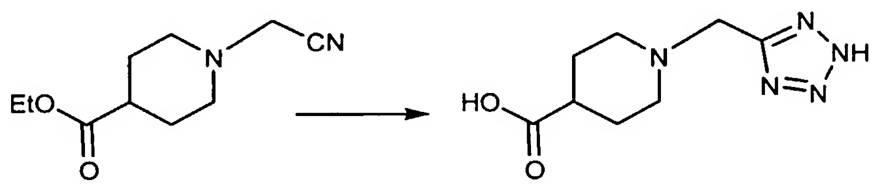
Step 1



38 **39**

To a stirred mixture of **38** (2.0 g, 12.5 mmol) and Na_2CO_3 (1.45 g, 13.7 mmol) in acetone (15 mL) was added chloroacetonitrile (1.05 g, 13.7 mmol) and the reaction mixture stirred for 3 h at room temperature. The solvent was removed in vacuo and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was dried (Na_2SO_4) and concentrated to give **37** (2.3 g, 94%) which was used as is.

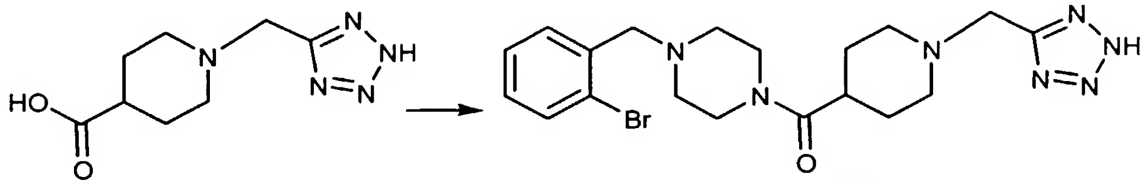
Step 2



39 **40**

To a solution of **39** (2.2 g, 11.2 mmol) in toluene (20 mL) was added n-Bu_3Sn (5.7 g, 16.8 mmol) and the reaction heated to reflux for 48 h. Additional n-Bu_3Sn (0.5 mL) was added and the reaction was stirred at reflux for 6 h and at room temperature for 18 h. The reaction was cooled to room temperature, 5 N NaOH (35 mL) and hexane (35 mL) were added and the reaction was stirred for 2 h. The aqueous phase was separated and neutralized with concentrated HCl. The water was evaporated in vacuo and the residue taken up in MeOH, filtered, and the filtrate concentrated to give **40** (3.6 g) which was used in the next step without further purification.

Step 3



40 41

In a manner similar to that described in Example 1, Step 2, compound **40** (0.2 g, 0.95 mmol) was converted to **41** (0.2 g, 47%). Mass spectrum : 448 (M+H).

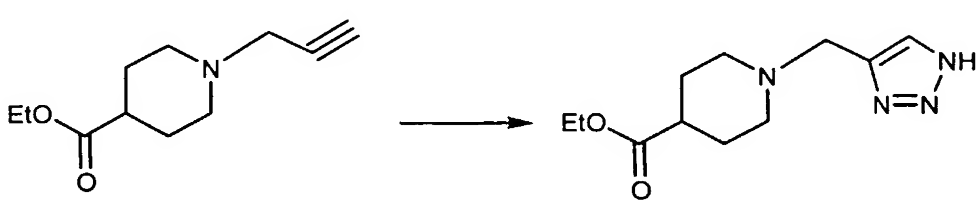
Example 8

Step 1

38 42

To a solution of **38** (2.57 g, 16 mmol) in THF (30 mL) was added propargyl bromide (1.34 g, 8.98 mmol) and the reaction heated to reflux overnight. After cooling to room temperature, the reaction was diluted with CH_2Cl_2 and washed with 1 N NaOH. The organic layer was dried and concentrated to give a residue which was purified by flash column chromatography (5% ethyl acetate in hexane) to give **42** (1.31 g, 75%). Mass spectrum: 196 (M+H).

Step 2

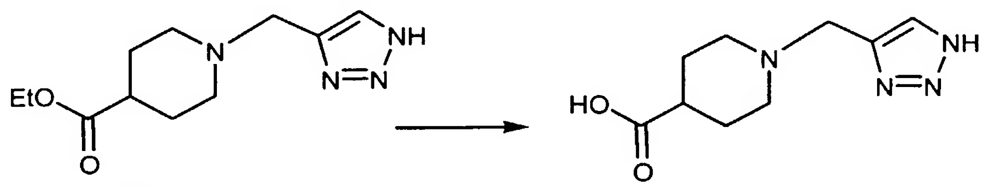


42 43

To a solution of **42** (0.5 g, 2.56 mmol) in toluene (10 mL) was added trimethylsilyl azide (0.62 g, 5.12 mmol) and the reaction was heated to reflux for 18 h. The reaction was cooled to room temperature, additional trimethylsilyl azide was added (0.7 mL). The reaction was stirred at 50° C for 8 days and 110° C for 10 days. The solvent was evaporated in vacuo, MeOH (100 mL) was added, and the MeOH

removed in vacuo. The residue so obtained was chromatographed (4% MeOH in ethyl acetate) to give **43** (0.5 g, 82%) Mass spectrum: 239 (M+H).

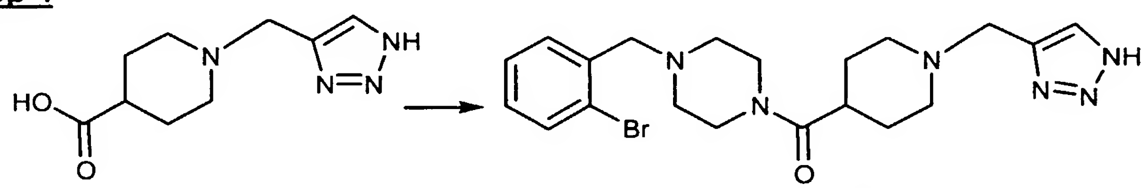
Step 3



43 **44**

In a manner similar to that described in Example 2, Step 4, Compound **43** (0.5 g, 2.1 mmol) was converted to compound **44** (0.44 g, 100%).

Step 4

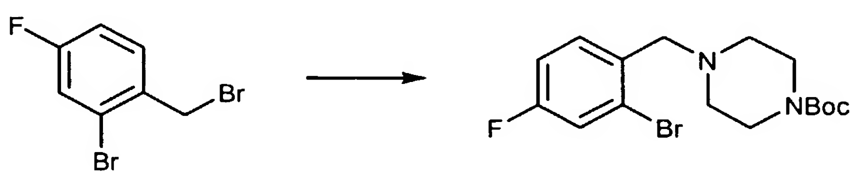


44 **45**

In a manner similar to that described in Example 1, Step 2, **44** (0.25 g, 1.2 mmol) and **21** (0.36, 1.4 mmol) were converted to **45** (0.11 g, 20%). Mass spectrum: 447 (M+H).

Example 9

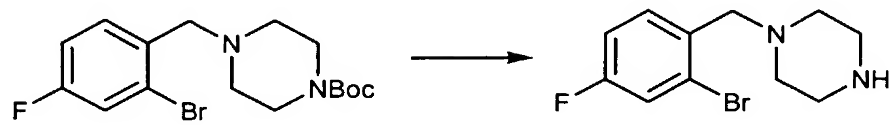
Step 1



46 **47**

A solution of compound **46** (2 g, 7.5 mmol), **19** (1.6 g, 8.2 mmol) and triethylamine (3.1 mL) in toluene (30 mL) was heated to reflux overnight. The solvent was evaporated and the residue partitioned between ethyl acetate and saturated $NaHCO_3$. The organic layer was dried and concentrated and the residue purified by flash column chromatography (30% ethyl acetate in hexane) to give **47** (1.6 g, 78%).

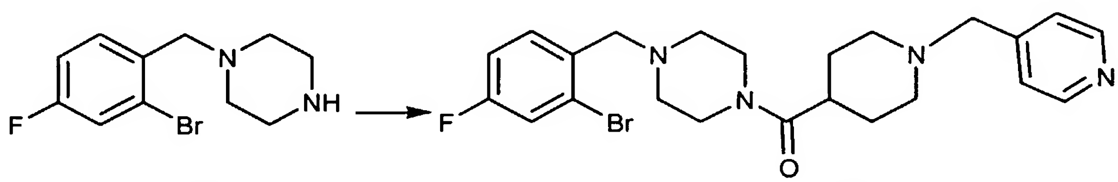
Step 2



47 48

In a manner similar to that described in Example 1, Step 3, **47** (1.6 g, 4.3 mmol) was converted to **48** (1.5 g, 100%).

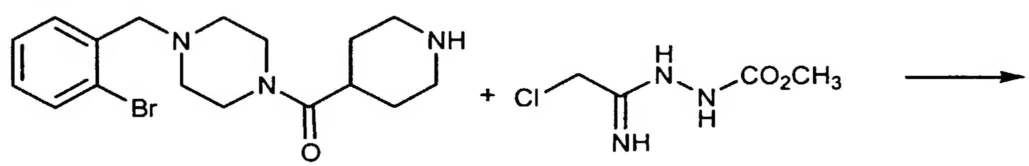
Step 3



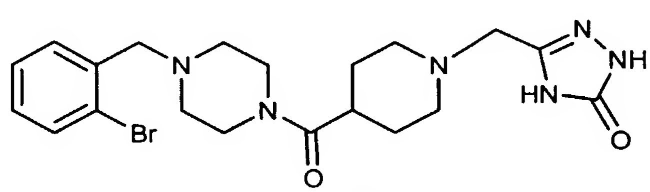
48 49

In a manner similar to that described in Example 1, Step 2, **48** (0.38 g, 1.1 mmol) was converted to **49** (0.15 g, 35%). Mass spectrum: 475 (M+H).

Example 10



32 50

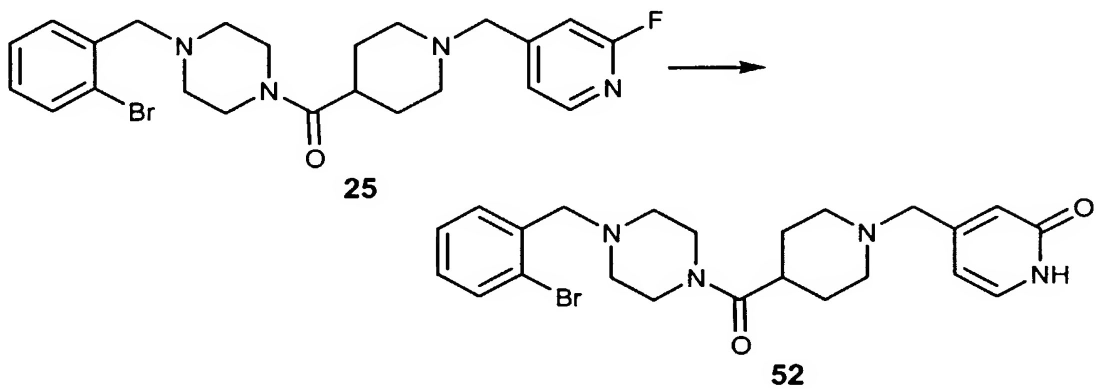


51

To a suspension of **32** (0.5 g, 1.14 mmol) in acetonitrile (5 mL) was added diisopropylethylamine (0.59 g, 4.56 mmol) followed after 10 min by **50** (0.23 g, 1.37 mmol). The mixture was stirred at room temperature for 48 h. The acetonitrile was removed, xylene (10 mL) was added and the reaction refluxed overnight. The reaction was cooled, diluted with ethyl acetate and washed with water. The organic

layer was dried and concentrated and chromatographed (10% to 20% MeOH in ethyl acetate) to give **51** (0.13 g, 25%). Mass spectrum: 463 (M+H).

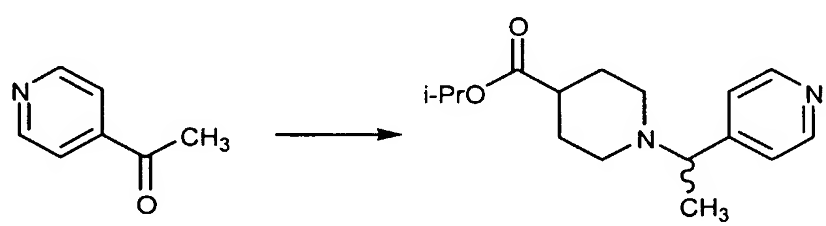
Example 11



A solution of **25** (0.13 g, 0.27 mmol) in 1:1 5% HCl in DME/water (4 mL) was heated to 60° C for 6 h. The reaction was cooled to room temperature, saturated $NaHCO_3$ and solid NaCl was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried, concentrated and the residue purified by flash column chromatography (5-10% NH_3/MeOH in CH_2Cl_2) to give **52** (40 mg, 31%). Mass spectrum: 473 (M+).

Example 12

Step 1

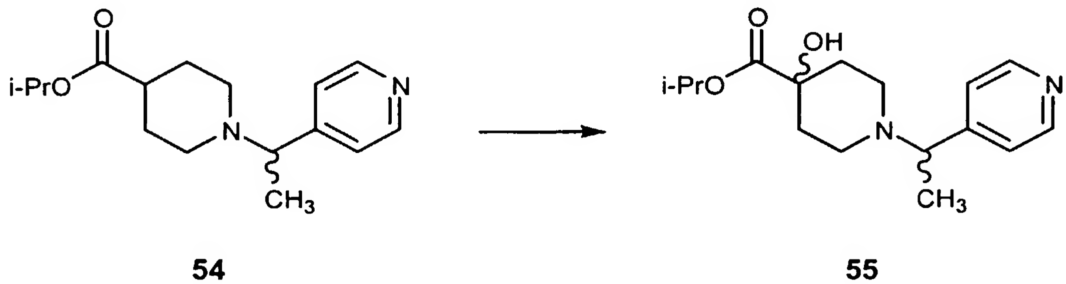


53 54

Compound **53** (3.6 g, 29.1 mmol), ethyl isonipecotate (5.8 g, 36.4 mmol) and $Ti(OiPr)_4$ (10.3 g, 36.4 mmol) were combined and stirred at room temperature overnight. CH_2Cl_2 (100 mL) was added followed by $NaBH(OAc)_3$ (8.6 g, 40.8 mmol) and the reaction stirred overnight. Saturated $NaHCO_3$ was added and the mixture filtered through Celite. The filter cake was washed with additional CH_2Cl_2, and the

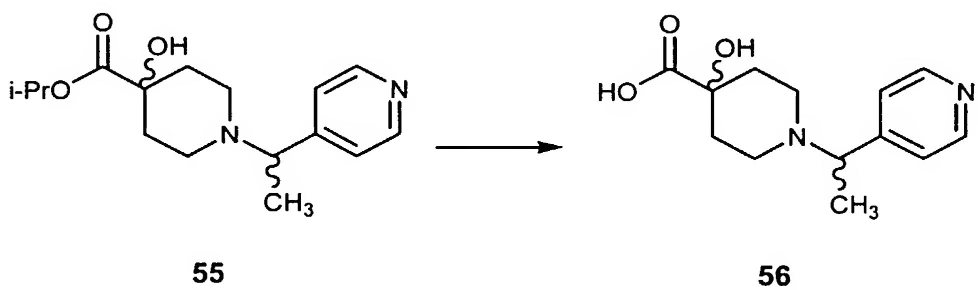
combined filtrates were washed with saturated $NaHCO_3$ and dried. Concentration gave a residue which was purified by flash column chromatography (8% MeOH in ethyl acetate) to give **54** (5 g, 83%). Mass spectrum: 277 (M+H).

Step 2



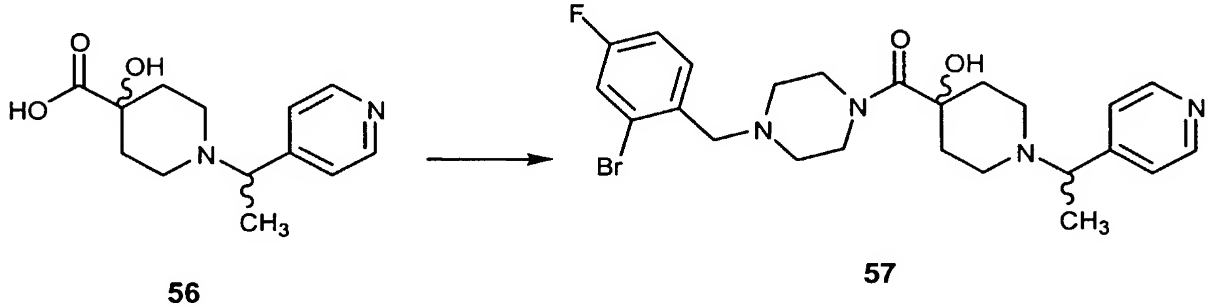
In a manner similar to that described in Example 4, Step 2, **54** (1 g, 3.6 mmol) was converted to **55** (0.4 g, 37%). Mass spectrum: 293 (M+H).

Step 3



In a manner similar to that described in Example 2, Step 4, **55** (0.4 g, 1.4 mmol) was converted to **56** (0.4 g, 100%).

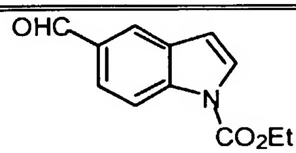
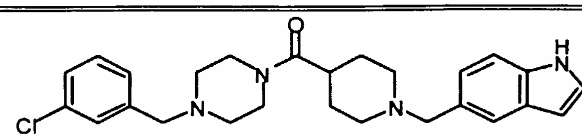
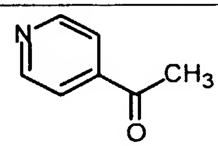
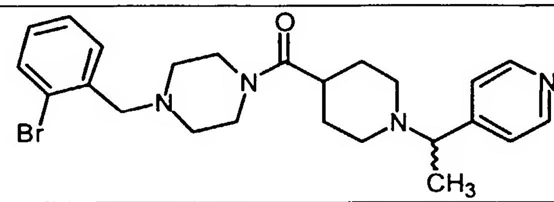
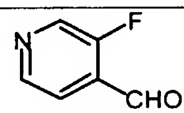
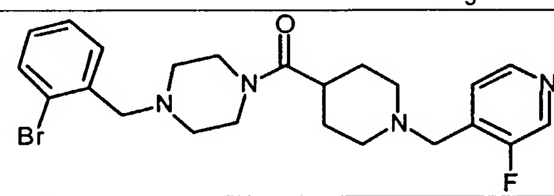
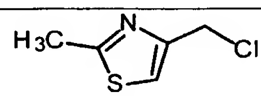
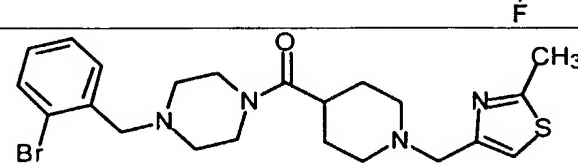
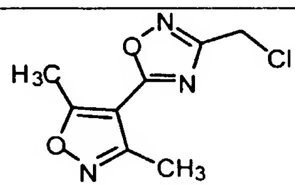
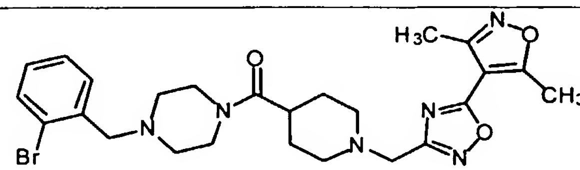
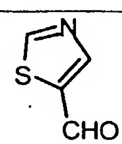
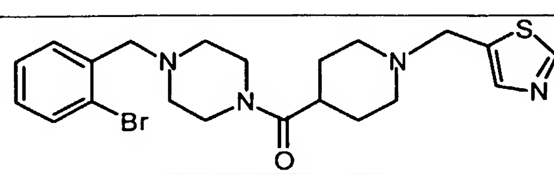
Step 4

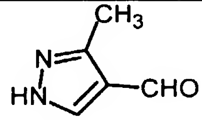
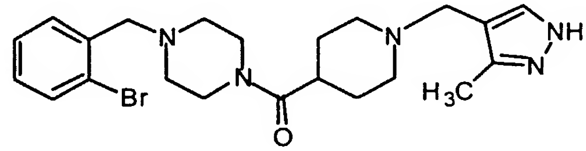
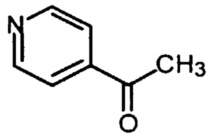
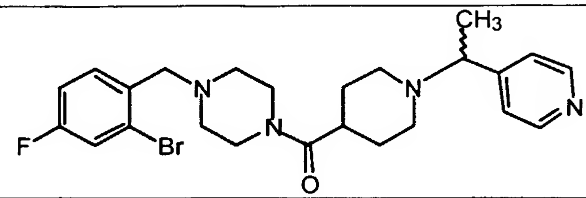
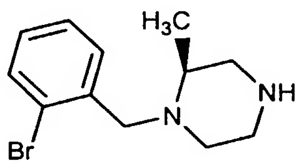
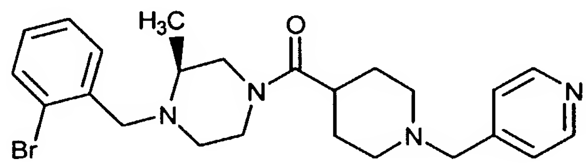
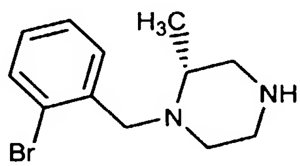
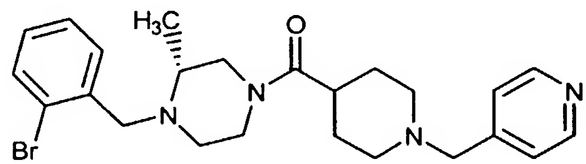


In a manner similar to that described in Example 1, Step 2, **56** (0.38 g, 1.6 mmol) was converted to **57** (0.36 g, 47%). Mass spectrum: 505 (M+H).

Using the procedures described in Examples 1 - 12, the compounds in Table 1 were synthesized:

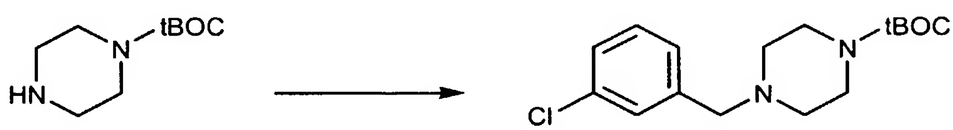
TABLE 1

Compound Number	Starting Material	Product
58		
59		
60		
61		
62		
63		

64		
65		
52		
53		

Example 13

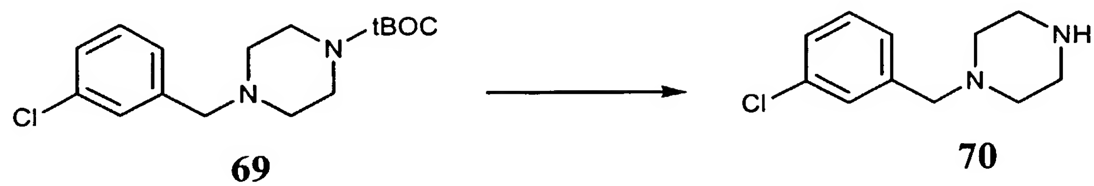
Step 1



68 **69**

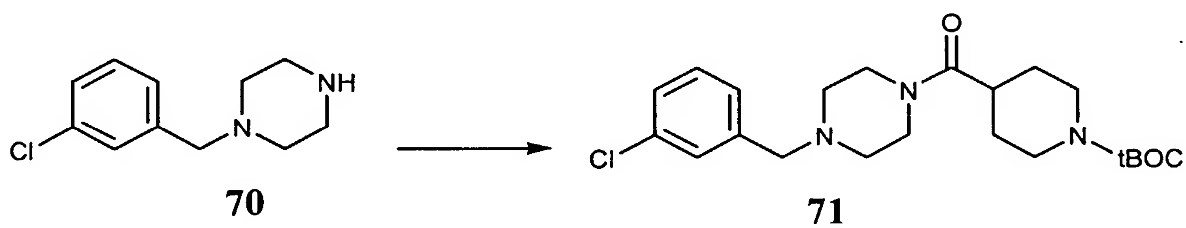
Dissolved amine **68** (25.0 g, 0.134 mol) in CH_2Cl_2 (500 mL) and added 3 A sieves (25 g), 3-chlorobenzaldehyde (28.3 g, 0.201 mol), and sodium triacetoxyborohydride (42.6 g, 0.201 mol). Stirred at 23° C for 16 h and filtered. Washed filtrate with saturated $NaHCO_3$ then saturated NaCl. Dried organic extract ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 20% EtOAc-hexane) to give 31.0 g (0.100 mol, 74%) of the product **69** as a yellow oil. MS (ES for M+1): m/e 312.

Step 2



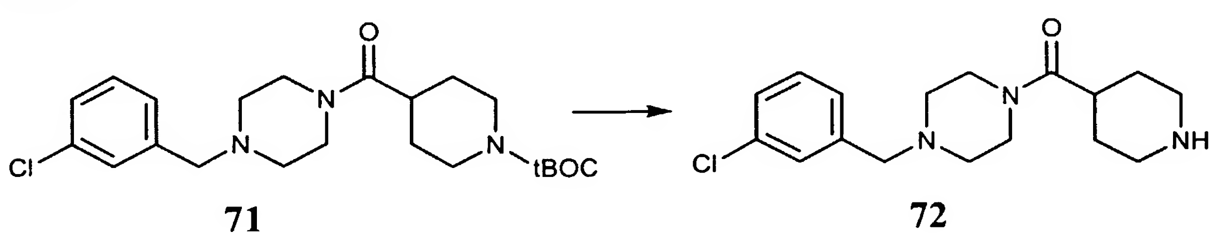
Dissolved compound **69** (27.0 g, 0.087 mol) in CH_2Cl_2 (500 mL) and added 1.0 N HCl in ether (275 mL, 0.275 mol). Stirred at 23° C for 96 h. Filtered and washed with ether to give 20.0 g of the dihydrochloride salt of compound **70**. Dissolved the dihydrochloride salt in 1 N NaOH (500 mL) and extracted with EtOAc. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 14.9 g (0.071 mol, 82%) of the product **70** as a yellow oil. MS (ES for M+1): m/e 211.

Step 3



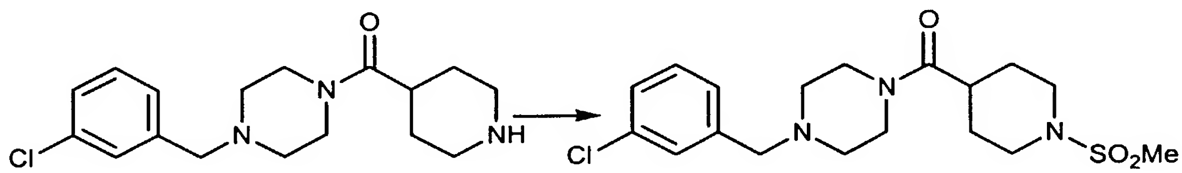
Combined compound **70** (13.03 g, 0.062 mol), N-tBOC-isonipecotic acid (21.38 g, 0.093 mol), HOBT (16.28 g, 0.12 mol), and DEC (23.01 g, 0.12 mol) in CH_2Cl_2 (400 mL). Stirred at 23° C for 4 h. Added 2 N NaOH and extracted with CH_2Cl_2. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 2% MeOH with NH_3-CH_2Cl_2) to give 25.0 g (0.059 mol, 95%) of the product **71** as a yellow oil. MS (ES for M+1): m/e 422.

Step 4



Dissolved compound **71** (20.0 g, 0.048 mol) in CH_2Cl_2 (250 mL) and cooled to 0° C. Added TFA (50 mL) and stirred at 23° C for 3 h. Concentrated, added 6.25 N NaOH, and extracted with CH_2Cl_2. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 5% MeOH with NH_3-CH_2Cl_2) to give 7.18 g (0.022 mol, 47%) of the product **72** as a yellow oil. MS (ES for M+1): m/e 322.

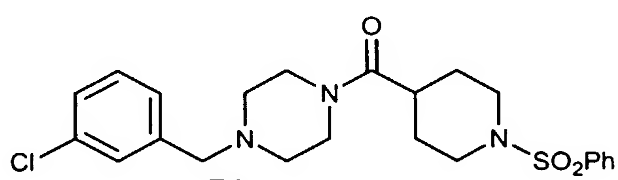
Step 5



72 **73**

Dissolved compound **72** (255 mg, 0.79 mmol) in CH_2Cl_2 (10 mL) and cooled to 0° C. Added triethylamine (158 mg, 0.22 mL, 1.56 mmol) and mesyl chloride (115 mg, 0.078 mL, 1.01 mmol). Warmed to 23° C and stirred for 16 h. Added saturated $NaHCO_3$ and extracted with CH_2Cl_2. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 2% MeOH with NH_3-CH_2Cl_2) to give 164 mg (0.41 mmol, 52%) of the product **73** as a white foam. MS (ES for M+1): m/e 400.

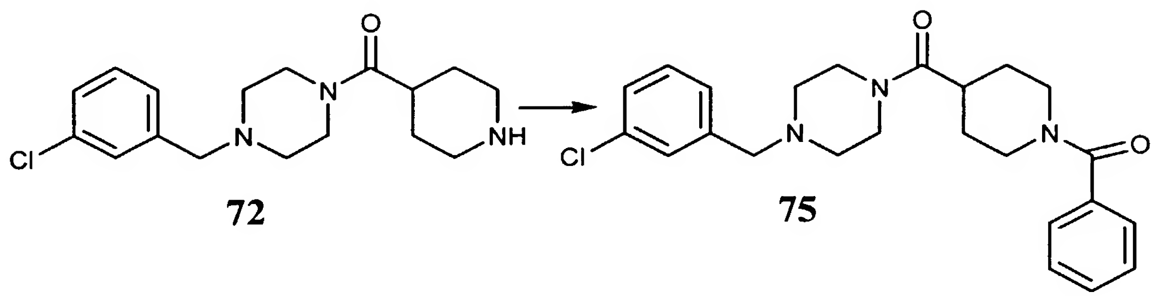
Following the above procedure compound 74 was prepared:



74

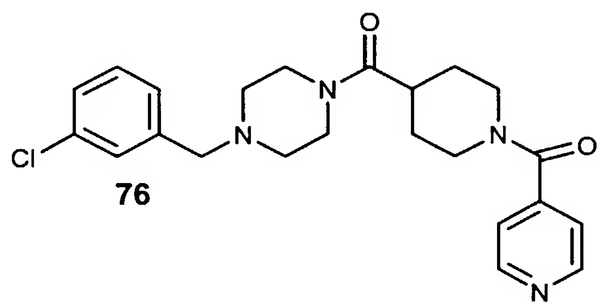
(MS(ES) 462 (M+1)).

Example 14



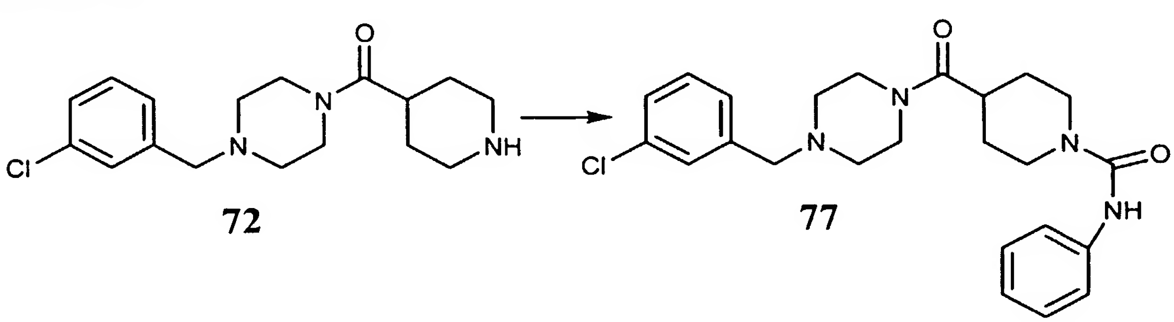
Dissolved compound **72** (250 mg, 0.78 mmol) and triethylamine (158 mg, 0.22 mL, 1.56 mmol) in CH_2Cl_2 (10 mL) and cooled to 0° C. Added benzoyl chloride (142 mg, 0.12 mL, 1.01 mmol). Warmed to 23° C and stirred for 16 h. Added saturated $NaHCO_3$ and extracted with CH_2Cl_2. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 3% MeOH with NH_3-CH_2Cl_2) to give 191 mg (0.45 mmol, 58%) of the product **75** as a white foam. MS (ES for M+1): m/e 426.

Following the above procedure compound 76 was prepared:



(MS(ES) 427 (M+1)).

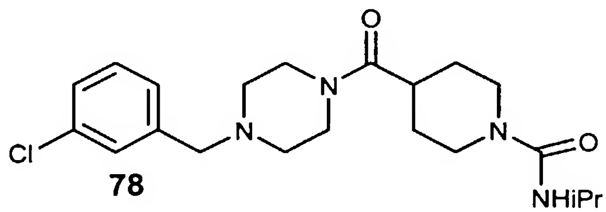
Example 15



Dissolved compound **72** (250 mg, 0.78 mmol) and triethylamine (158 mg, 0.22 mL, 1.56 mmol) in dry THF (10 mL). Added phenylisocyanate (120 mg, 0.11 mL, 1.0

mmol) and stirred at 23° C for 16 h. Added water and extracted with EtOAc. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 3% MeOH with NH_3-CH_2Cl_2) to give 170 mg (0.39 mmol, 50%) of the product **77** as a white foam. MS (ES for M+1): m/e 441.

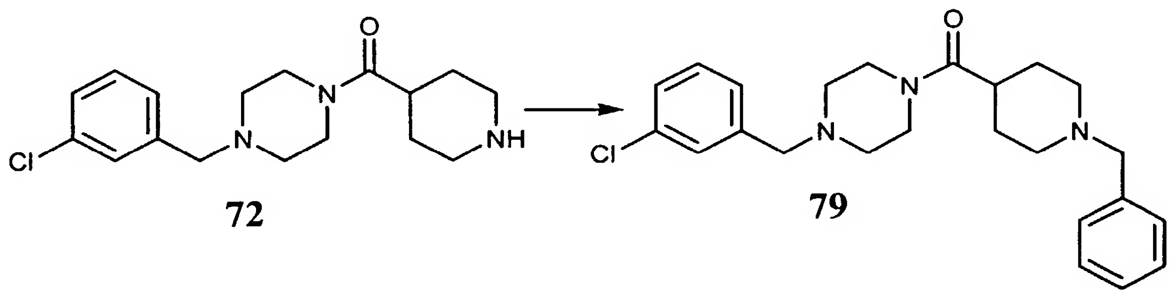
Following the above procedure compound 78 was prepared:



78

(MS(ES) 407 (M+1)).

Example 16

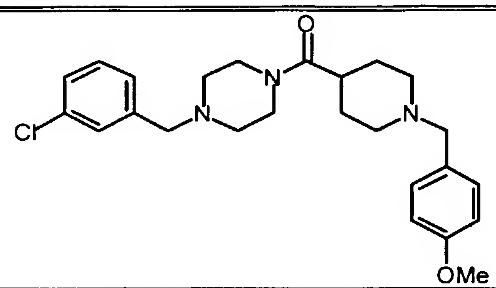
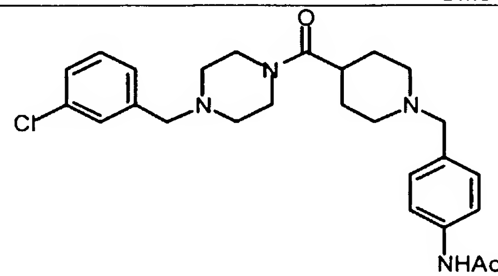
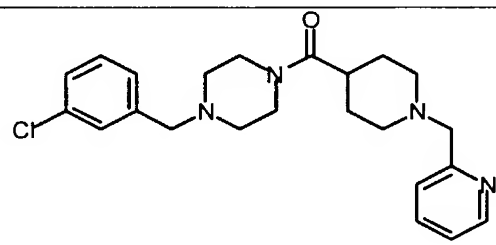
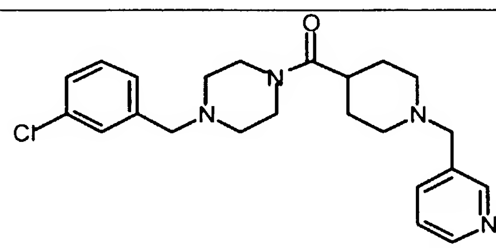
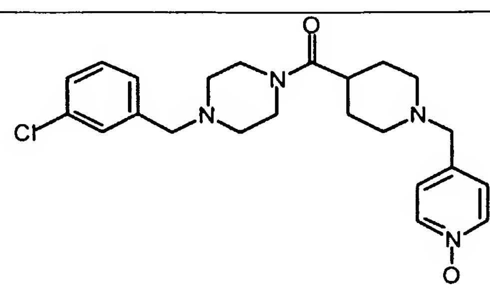


72 79

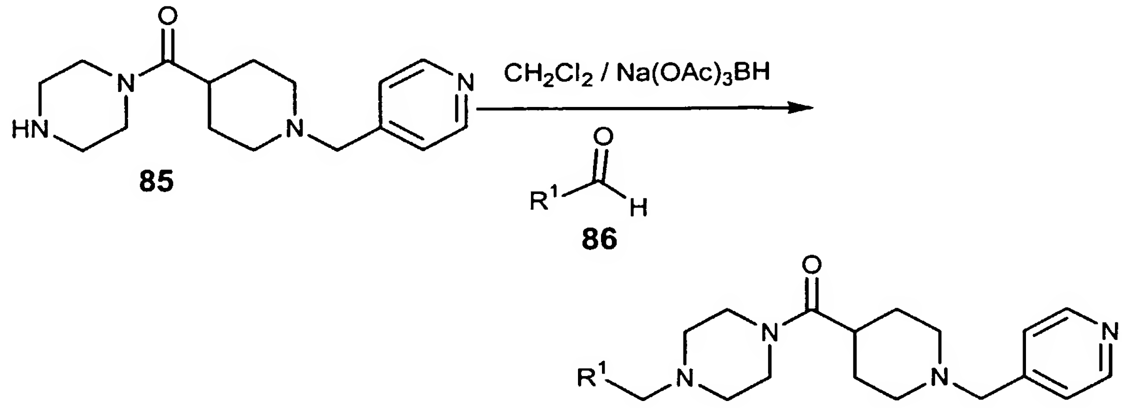
Combined compound **72** (550 mg, 1.71 mmol), benzaldehyde (109 mg, 1.03 mmol), 0.5 g of crushed 3A sieves, and sodium triacetoxyborohydride (347 mg, 1.64 mmol) in 2:1 CH_2Cl_2:EtOH (15 mL). Stirred at 23° C for 16 h. Added saturated $NaHCO_3$ and extracted with CH_2Cl_2. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 3% MeOH with NH_3-CH_2Cl_2) to give 260 mg (0.63 mmol, 37%) of the product **79** as a white foam. MS (ES for M+1): m/e 412.

Following the above procedure the compounds in Table 2 were prepared.

TABLE 2

Compound Number	Compound	MS (ES)
80		442 (M+1)
81		469 (M+1)
82		413 (M+1)
83		413 (M+1)
84		429 (M+1)

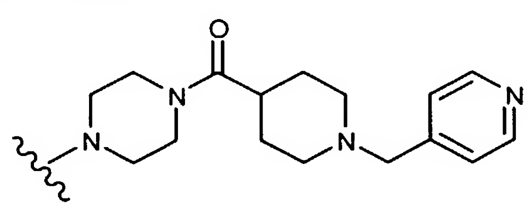
Example 17: General procedure for reductive amination, parallel synthesis.



87

A solution of the amine **85** (0.063 mmol) and the aldehyde **86** (0.32 mmol, 1.0 M in dichloroethane) is treated with $NaBH(OAc)_3$ (0.32 mmol, 0.5 M in dichloroethane) and placed on shaker for an average period of 18 h. Where needed more $NaBH(OAc)_3$ is added to force the reaction into completion. Amberlyst-15 resin (~100 mg) is added and the reaction mixture shaken for an additional hour while monitoring by TLC (10% NH_3 saturated methanol in CH_2Cl_2, R_f~0.3) to ensure no amine product remained in solution. The resin is filtered and alternately washed six times with MeOH and dichloroethane. The resin is extracted by stirring twice, for 30 min, with 2N NH_3/MeOH (2 ml) and rinsing twice with MeOH (2 ml). The combined extracts are concentrated in vacuo to provide the desired product **65**.

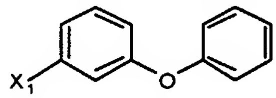
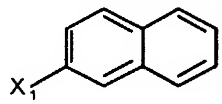
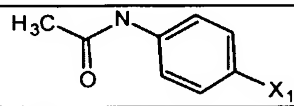
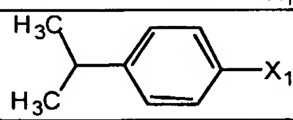
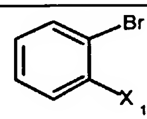
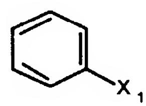
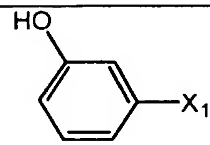
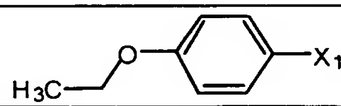
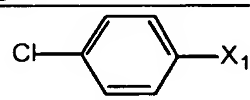
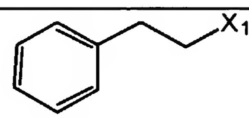
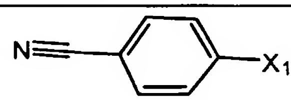
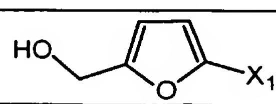
Using this procedure, the compounds listed in **Table 3** were synthesized. In **Table 3** X_1 represents the moiety:

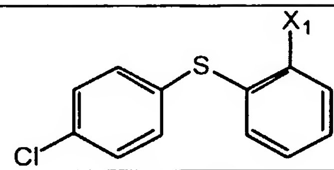
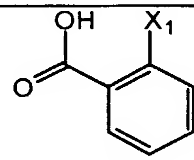
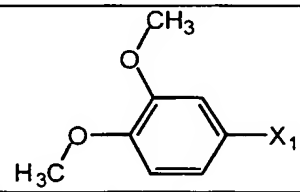
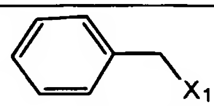
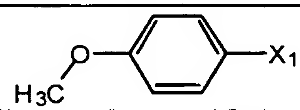
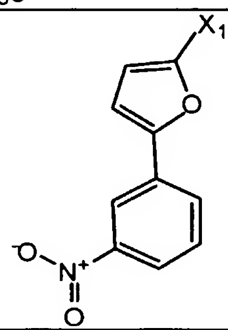
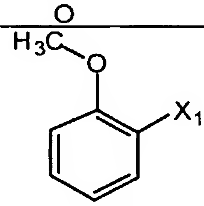
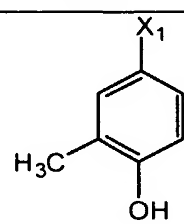


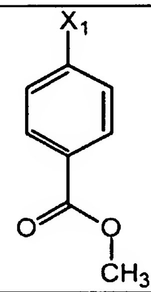
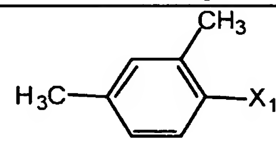
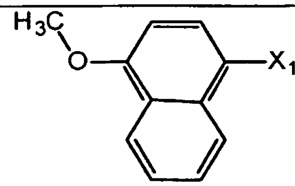
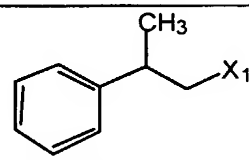
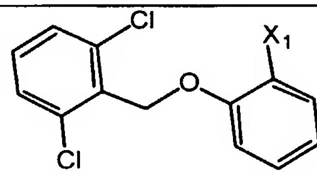
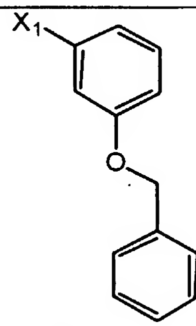
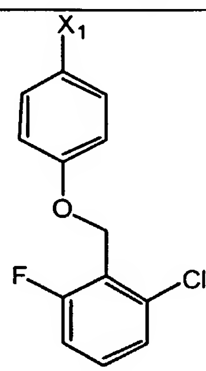
88

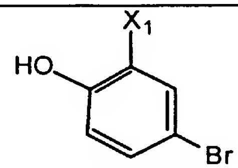
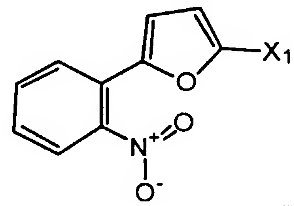
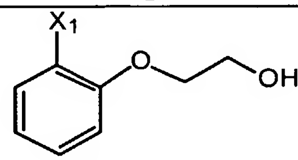
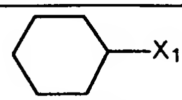
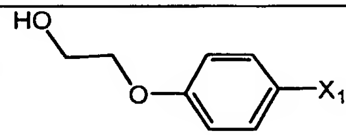
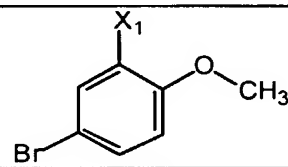
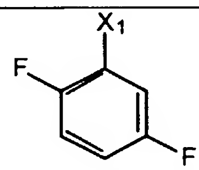
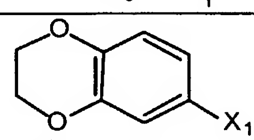
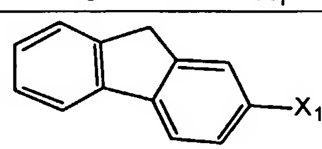
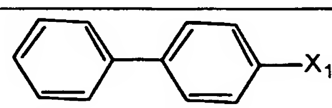
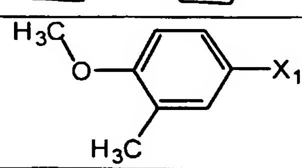
(i.e., the moiety **88** is compound **87** without the R^1CH_2-group).

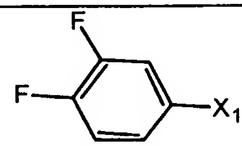
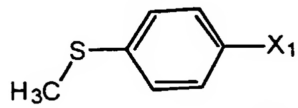
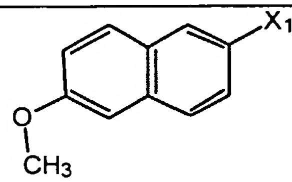
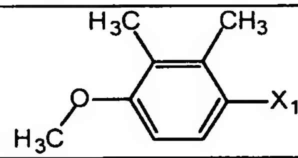
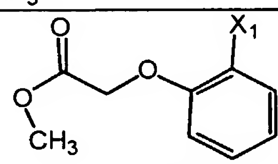
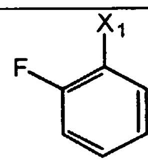
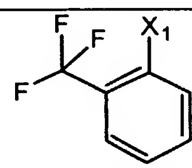
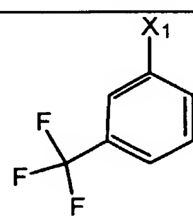
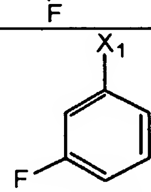
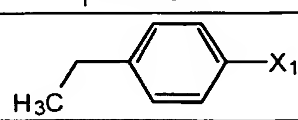
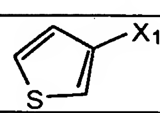
TABLE 3

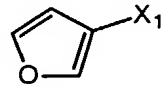
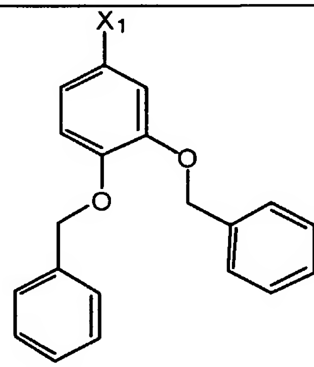
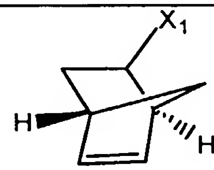
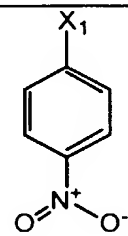
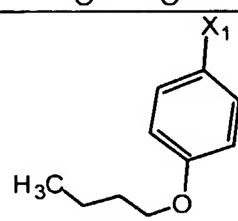
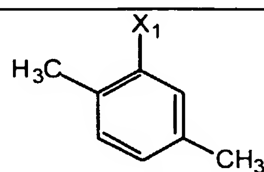
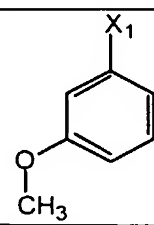
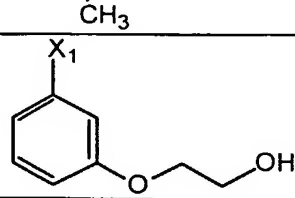
Compound No.	R^1	MS
89		471.1 (MH^+)
90		429.1 (MH^+)
91		436.1 (MH^+)
92		421.1 (MH^+)
93		459.1581 (MH^+)
94		379.1 (MH^+)
95		395.1 (MH^+)
96		423.1 (MH^+)
97		413.1 (MH^+)
98		407.1 (MH^+)
99		404.1 (MH^+)
100		399.1 (MH^+)

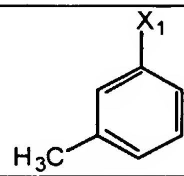
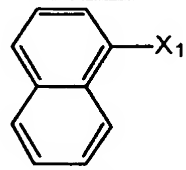
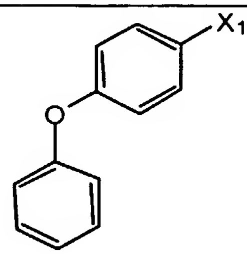
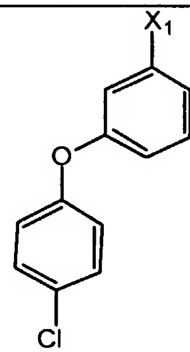
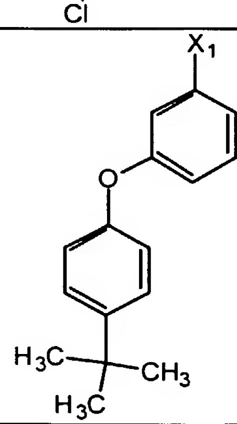
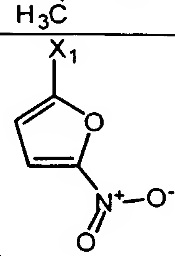
101		521.1 (M^+)
102		423.1 (MH^+)
103		439.1 (MH^+)
104		393.1 (MH^+)
105		409.1 (MH^+)
106		490.1 (MH^+)
107		409.1 (MH^+)
108		409.1 (MH^+)

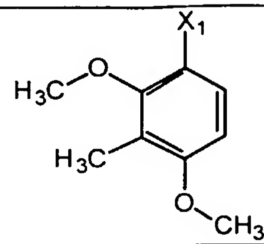
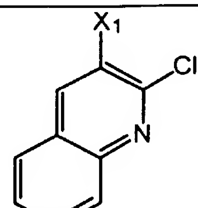
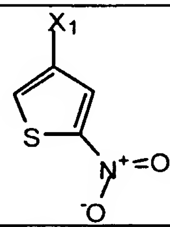
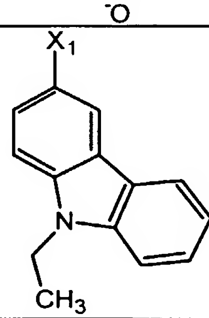
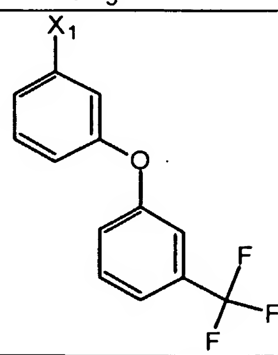
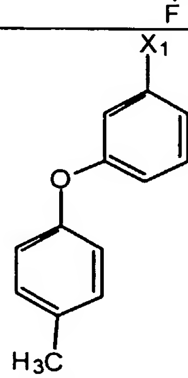
109		437.1 (MH$^+$)
110		407.1 (MH$^+$)
111		459.1 (MH$^+$)
112		421.1 (MH$^+$)
113		553.1 (M$^+$)
114		485.1 (MH$^+$)
115		537.1 (M$^+$)

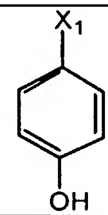
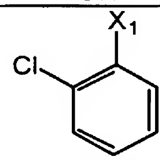
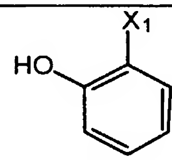
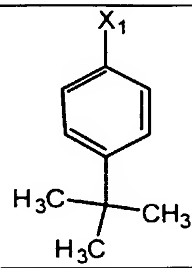
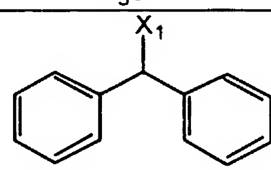
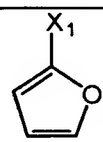
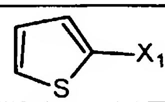
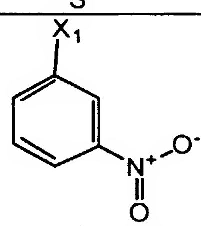
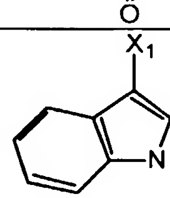
116		473.1 (M^+)
117		490.1 (MH^+)
118		439.1 (MH^+)
119		485.1 (MH^+)
120		439.1 (MH^+)
121		488.1 (MH^+)
122		415.1 (MH^+)
123		437.1 (MH^+)
124		467.1 (MH^+)
125		455.1 (MH^+)
126		423.1 (MH^+)

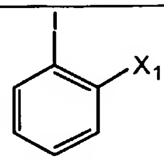
127		415.1 (MH^+)
128		425.1 (MH^+)
129		459.1 (MH^+)
130		437.1 (MH^+)
131		467.1 (MH^+)
132		397.1 (MH^+)
133		447.1 (MH^+)
134		447.1 (MH^+)
135		397.1 (MH^+)
136		407.1 (MH^+)
137		385.1 (MH^+)

138		369.1 (MH$^+$)
139		591.1 (MH$^+$)
140		395.1 (MH$^+$)
141		424.1 (MH$^+$)
142		451.1 (MH$^+$)
143		407.1 (MH$^+$)
144		409.1 (MH$^+$)
145		439.1 (MH$^+$)

146		393.1 (MH^+)
147		429.1 (MH^+)
148		471.1 (MH^+)
149		505.1 (M^+)
150		527.1 (MH^+)
151		414.1 (MH^+)

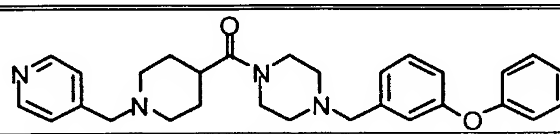
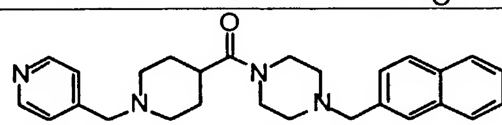
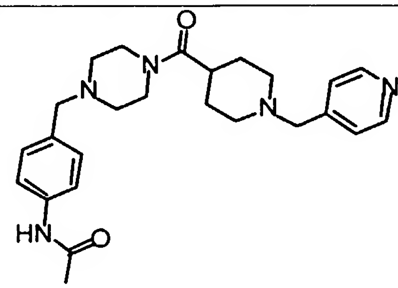
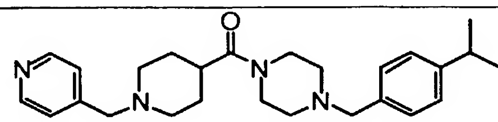
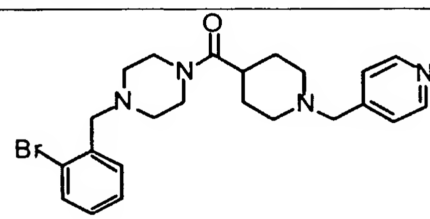
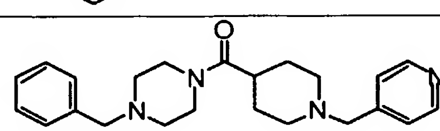
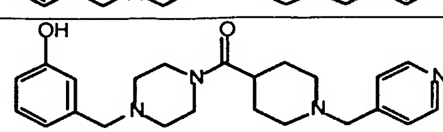
152		453.1 (MH$^+$)
153		464.1 (M$^+$)
154		430.1 (MH$^+$)
155		496.1 (MH$^+$)
156		539.1 (MH$^+$)
157		485.1 (MH$^+$)

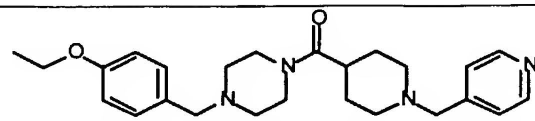
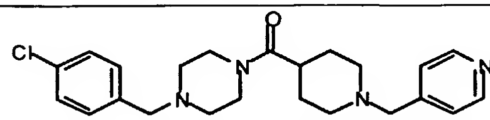
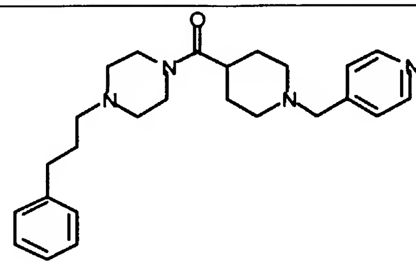
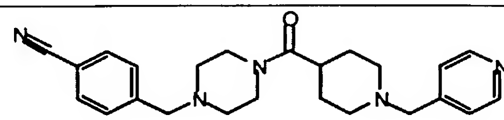
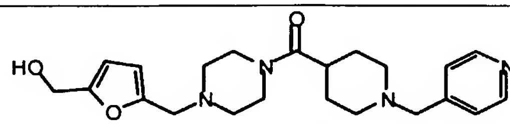
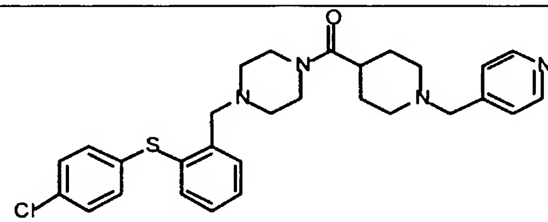
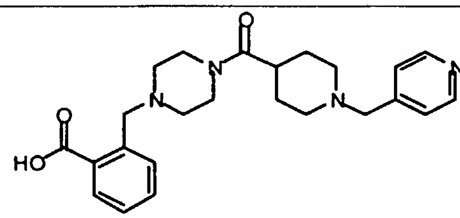
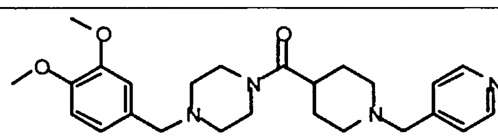
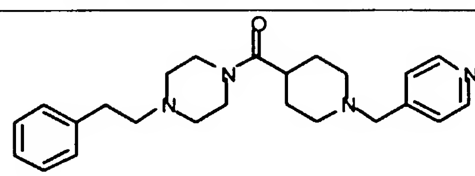
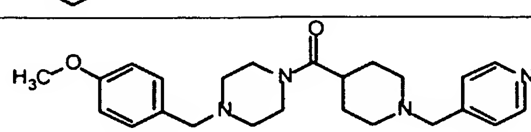
159		395.1 (MH^+)
160		413.1 (MH^+)
161		395.1 (MH^+)
162		435.1 (MH^+)
163		469.1 (MH^+)
164		369.1 (MH^+)
165		385.1 (MH^+)
166		424.1 (MH^+)
167		418.1 (MH^+)

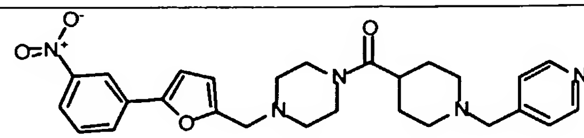
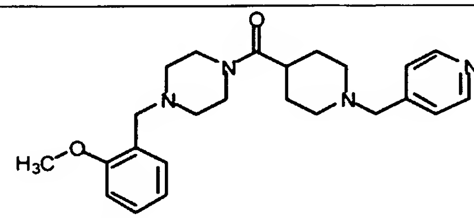
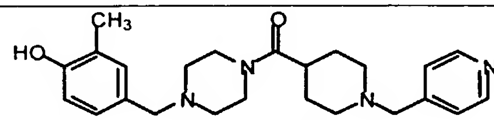
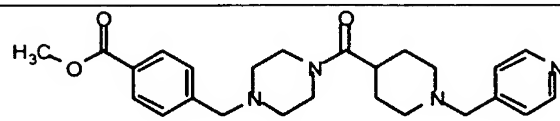
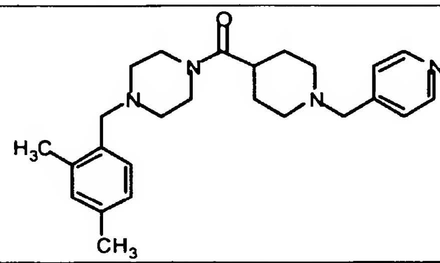
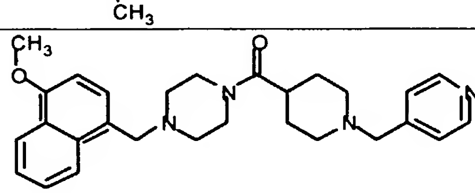
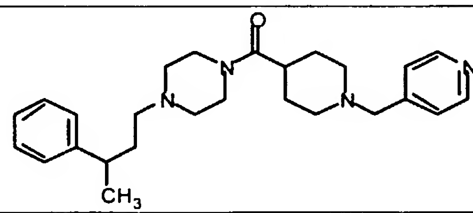
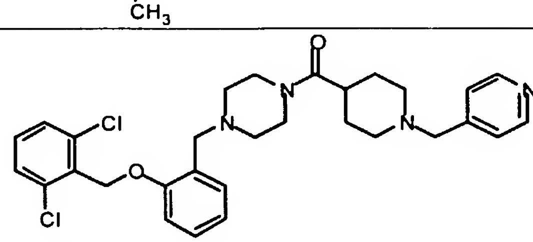
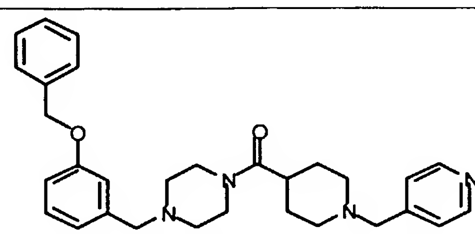
168		505 (MH^+)

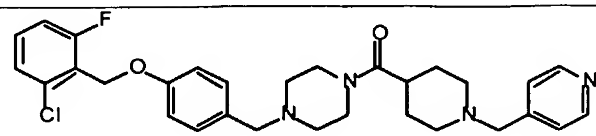
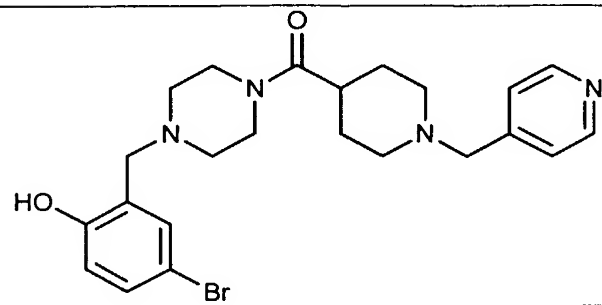
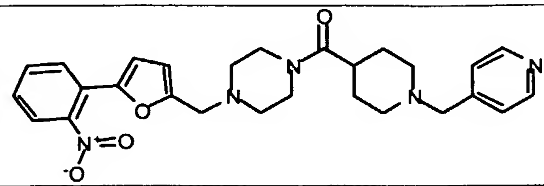
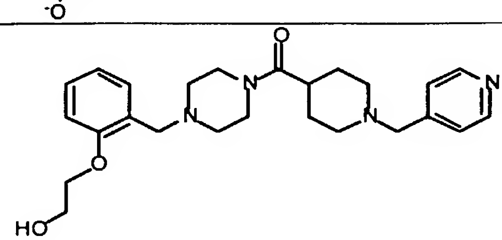
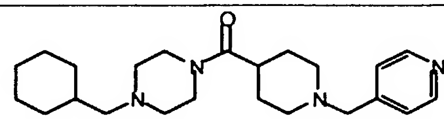
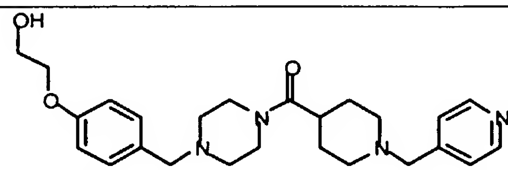
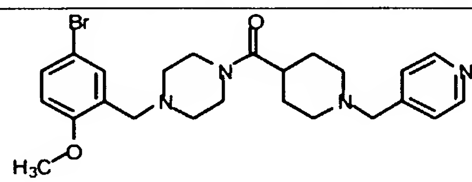
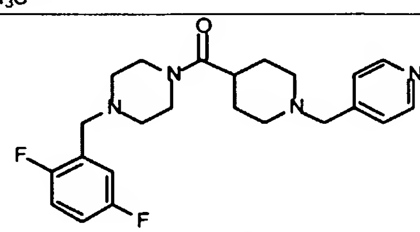
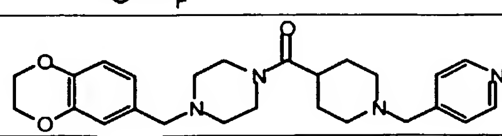
Thus, compounds in Table 3 have the formulas given in Table 4 below.

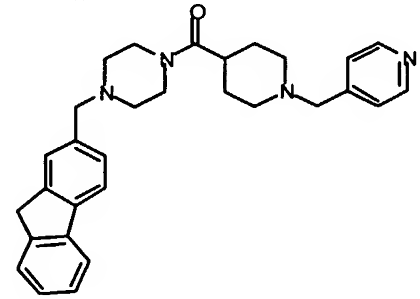
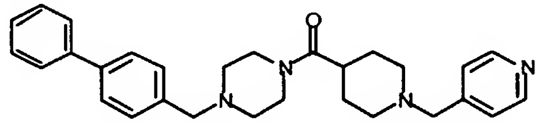
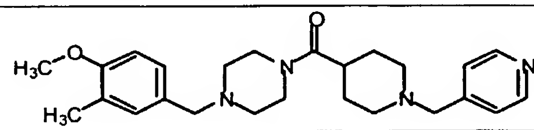
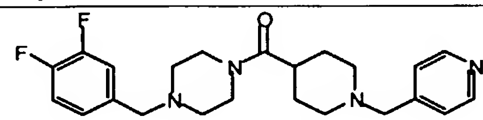
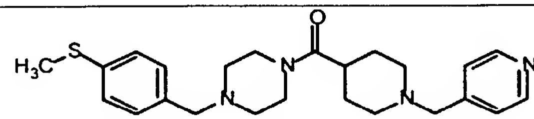
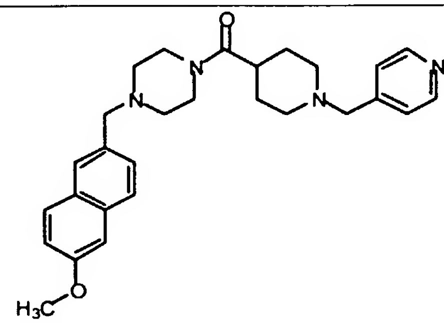
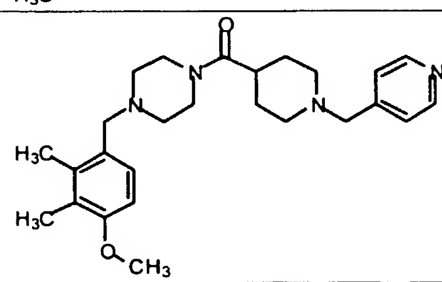
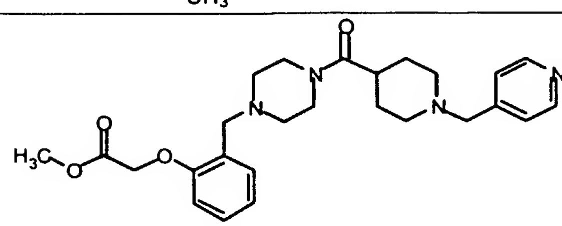
TABLE 4

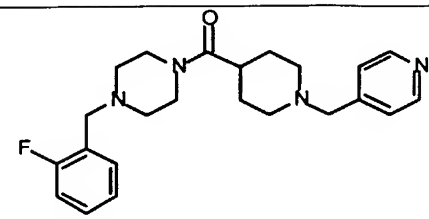
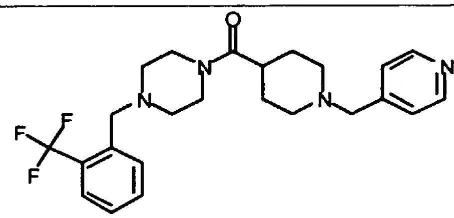
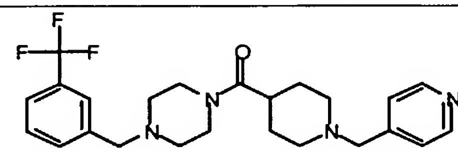
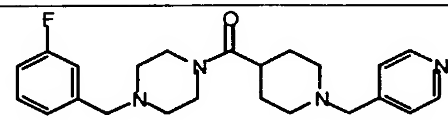
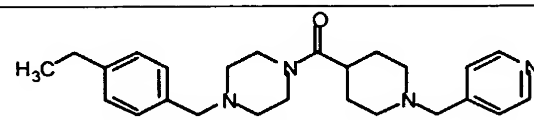
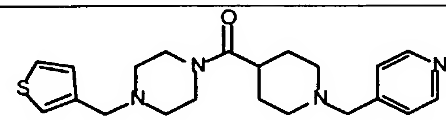
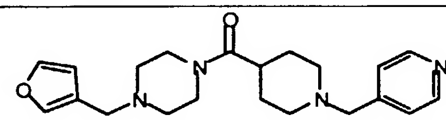
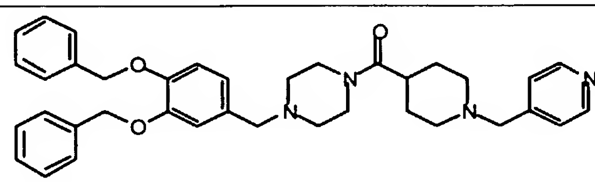
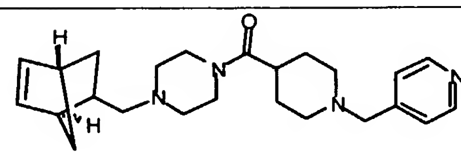
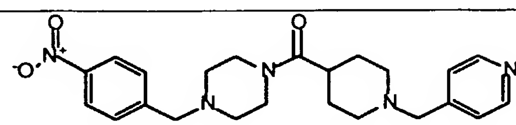
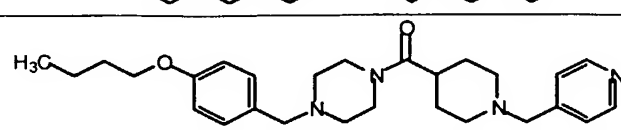
Compound No.	Structure
89	
90	
91	
92	
93	
94	
95	

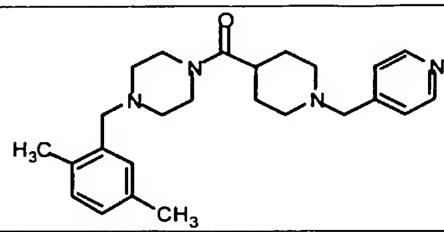
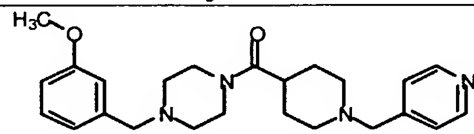
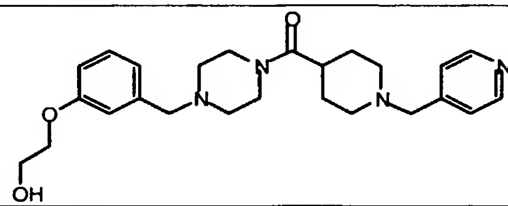
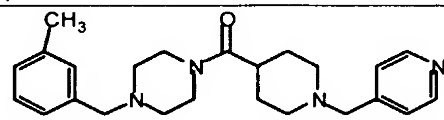
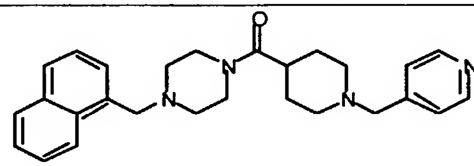
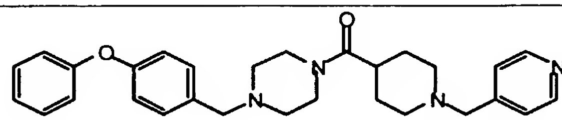
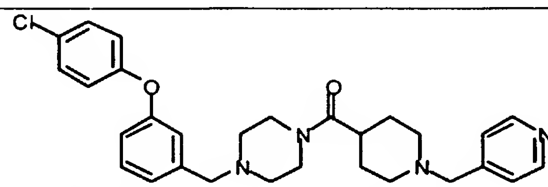
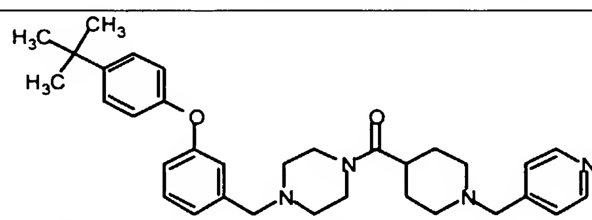
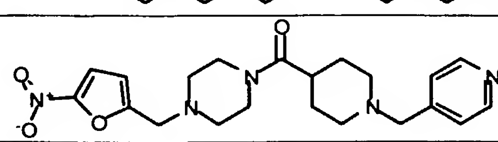
96	
97	
98	
99	
100	
101	
102	
103	
104	
105	

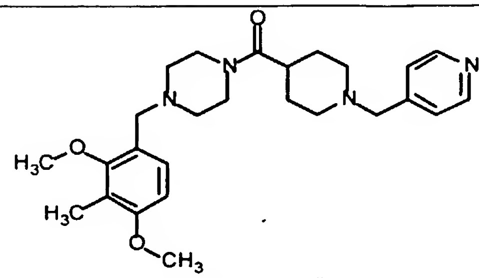
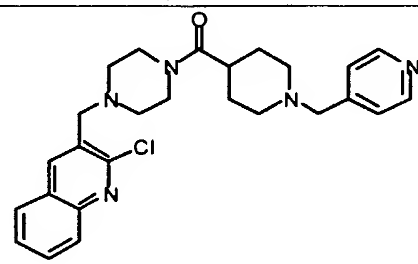
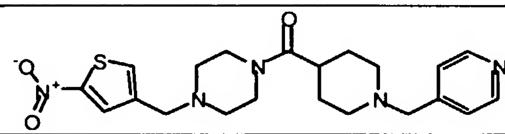
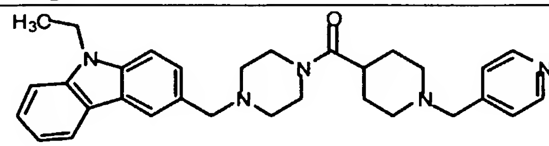
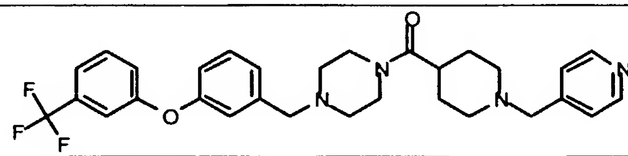
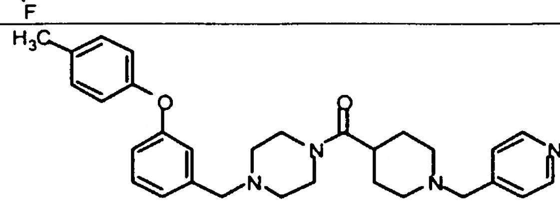
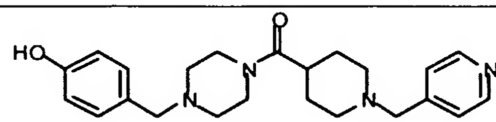
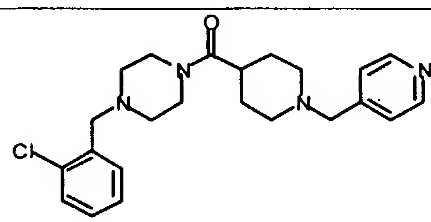
106	
107	
108	
109	
110	
111	
112	
113	
114	

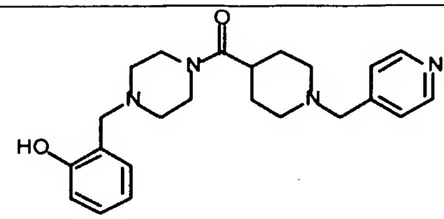
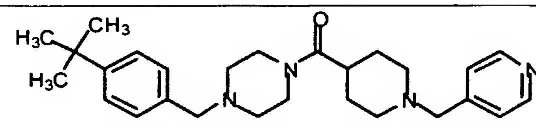
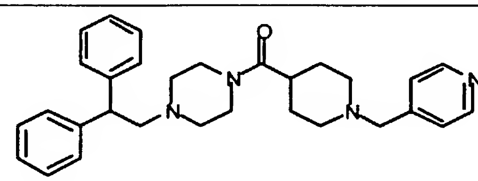
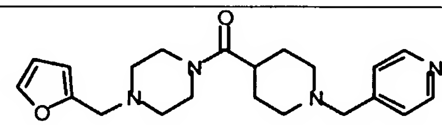
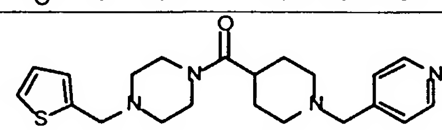
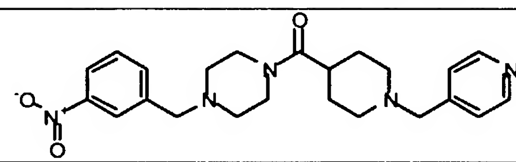
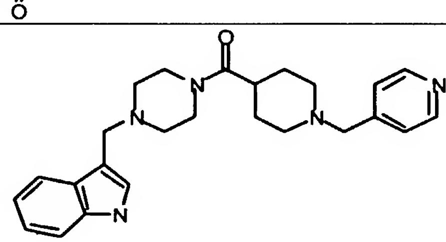
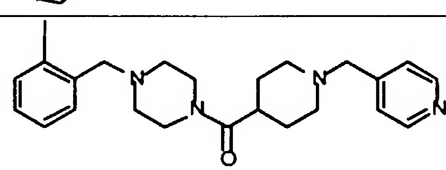
115	
116	
117	
118	
119	
120	
121	
122	
123	

124	
125	
126	
127	
128	
129	
130	
131	

132	
133	
134	
135	
136	
137	
138	
139	
140	
141	
142	

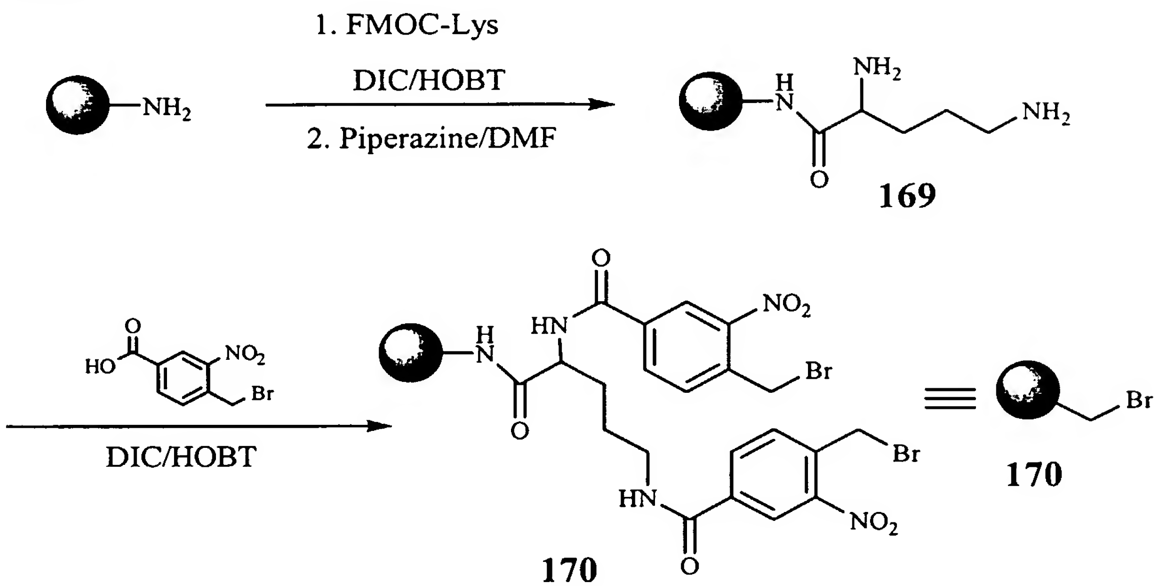
143	
142	
145	
146	
147	
148	
149	
150	
151	

152	
153	
154	
155	
156	
157	
159	
160	

161	
162	
163	
164	
165	
166	
167	
168	

Example 18: Library preparation on solid phase

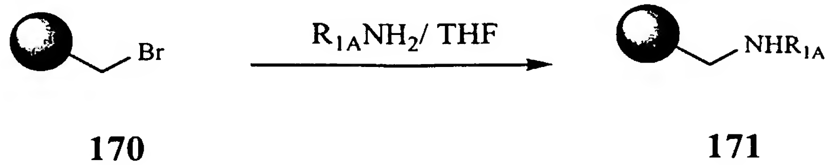
Scheme 1



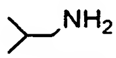
TentaGel amino resin (1 eq.) was placed in a reaction vessel, dichloromethane, FMOC-Lysine (2 eq.) and HOBT (2.2 eq.) were added followed by the addition of DIC (2eq.). The mixture was shaken at room temperature for 12 hours, then drained and the resin was washed with dichloromethane twice and DMF three times, and treated with 20% piperazine in DMF (v/v) for 30 minutes. The resin was then washed with DMF twice, methanol twice and dichloromethane three times, and dried overnight in *vacuo* to give amine resin **169**.

The amine resin **169** (1 eq.) was placed in a reaction vessel, dichloromethane, 4-bromomethyl-3-nitrobenzoic acid (2 eq.) and HOBT (2.2 eq.) were added followed by the addition of DIC (2eq.). The mixture was shaken at room temperature for 12 hours, then drained and the resin was washed with dichloromethane twice, methanol twice and dichloromethane three times, and dried overnight in *vacuo* to give bromoresin **170**.

Scheme 2



The bromo resin **170** was divided into **24** portions, and each (1eq.) was treated with an amine (see 172 to 196 below) (5eq.) in THF. The mixture was shaken at room temperature overnight, drained and the resin was washed with THF twice, DMF twice and dichloromethane three times, and dried overnight in *vacuo* to give amine resin **171**.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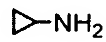
173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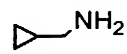
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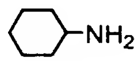
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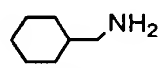
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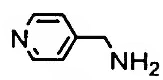
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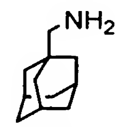
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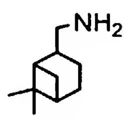
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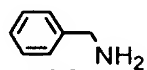
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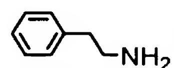
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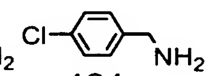
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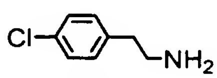
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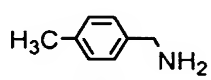
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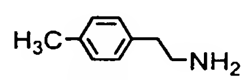
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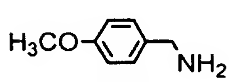
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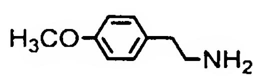
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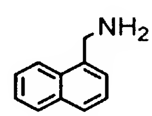
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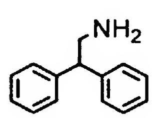
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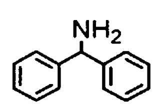
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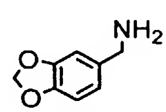
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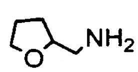
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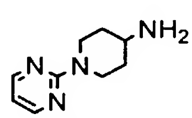
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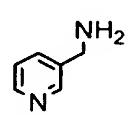
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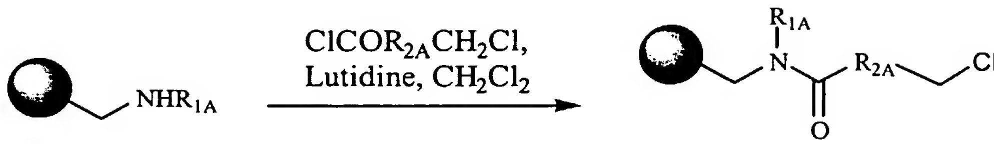
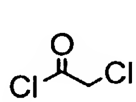
Scheme 3



171 **197**

The amine resin **171** was divided into **3** portions, and each (1 eq.) was treated with an acid chloride (see 198 to 200 below)(2 eq.) and 2,6-lutidine (4 eq.) in dichloromethane. The mixture was shaken at room temperature for 30 minutes, drained and the resin was washed with dichloromethane twice, methanol twice and dichloromethane three times, and dried overnight in *vacuo* to give chlororesin **197**.



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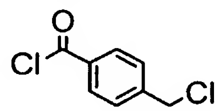

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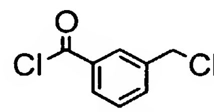
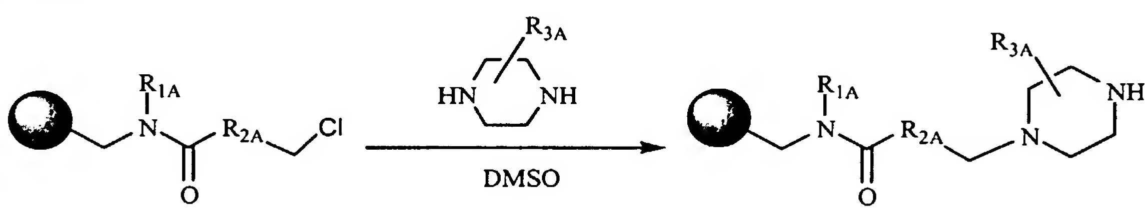


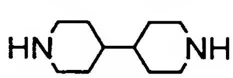
200

Scheme 4



197 **201**

The chlororesin **197** was divided into **7** portions, and each (1 eq.) was treated with an appropriate amine (see 202 to 208 below) (5 eq.) in DMSO. The mixture was shaken at room temperature overnight, drained and the resin was washed with methanol twice, dichloromethane twice, methanol twice and dichloromethane three times, and dried in *vacuo* to give amine resin **201**.



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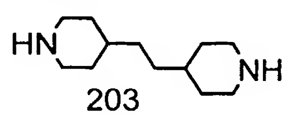

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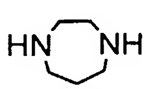

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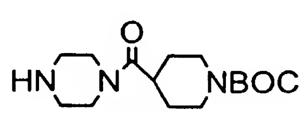

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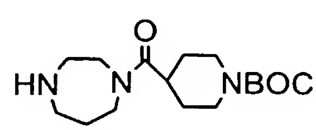

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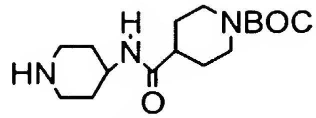
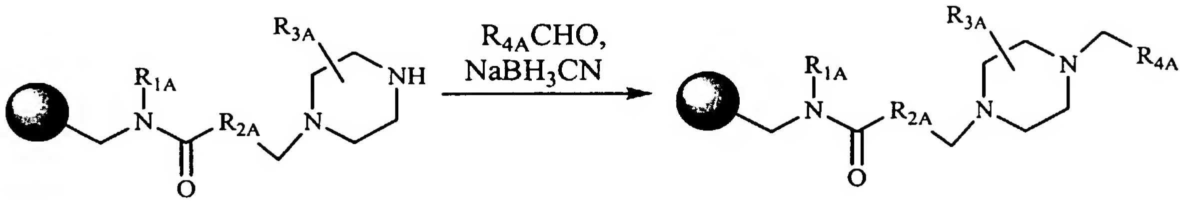


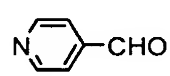
208

Scheme 5



201 209

The amine resin **201** was divided into **2** reaction vessels, and each was treated with 2% HOAc in DMF and an appropriate aldehyde (see 210-211 below). The mixture was shaken at room temperature for 30 minutes, and $NaBH_3CN$ was added to each reaction vessel. The mixture was shaken for overnight, drained, and the resin was washed with DMF twice, methanol three times and 10% HCl in methanol, and dried in *vacuo* to give resin **209**.



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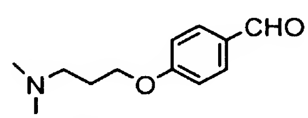
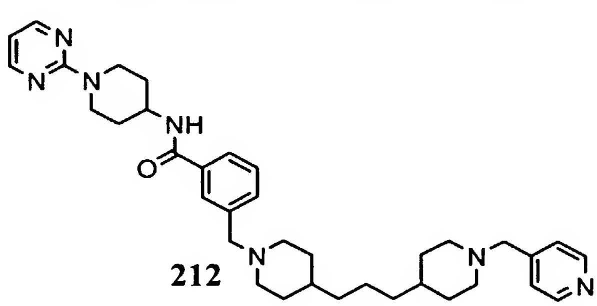


211

In the above Schemes, R_{1A} represents the substituents on R^1, R_{2A} represents R^1, R_{3A} represents R^{12} or R^{13}, and R_{4A} represents R^2.

Examples of compounds made by the above library procedure include:



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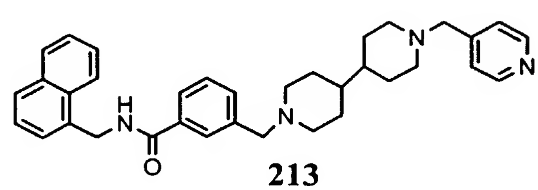

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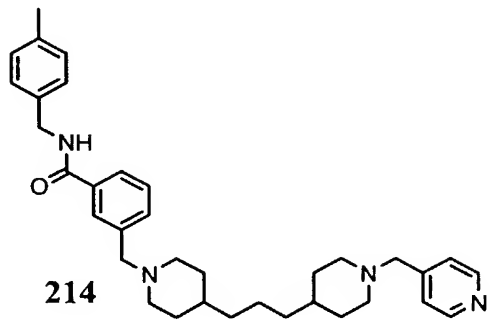

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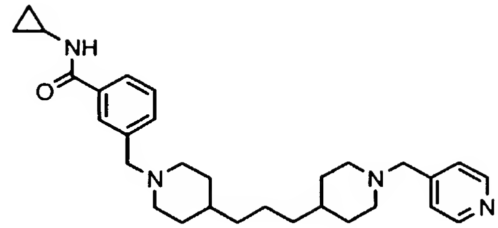

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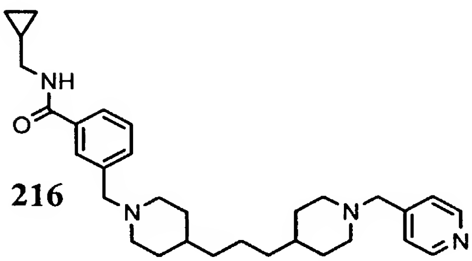

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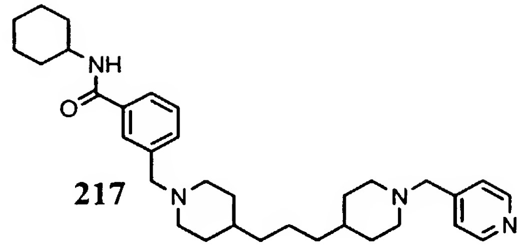

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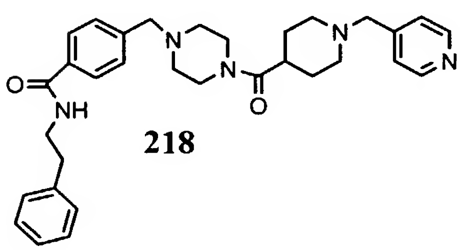

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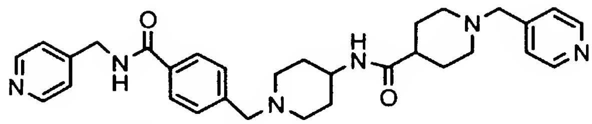

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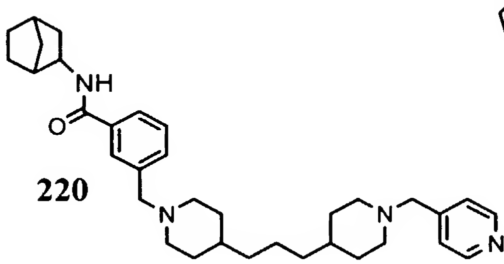

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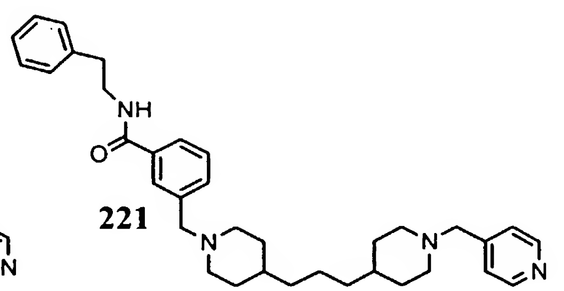

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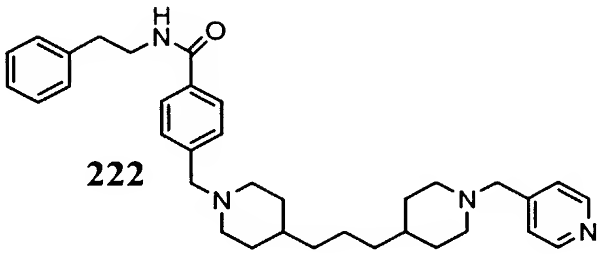

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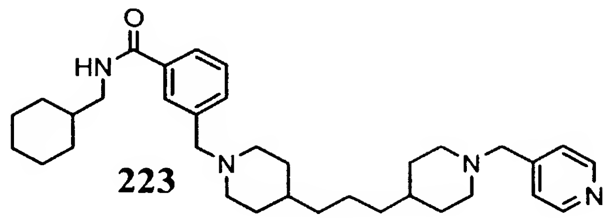

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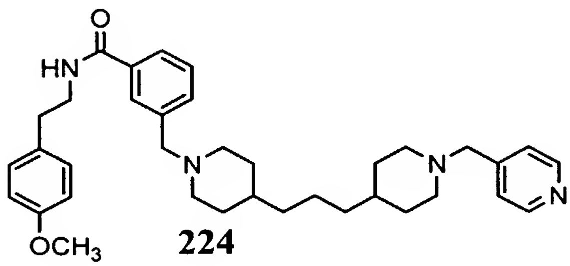

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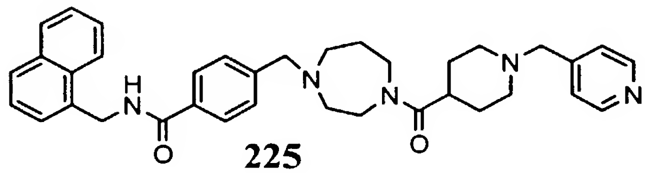

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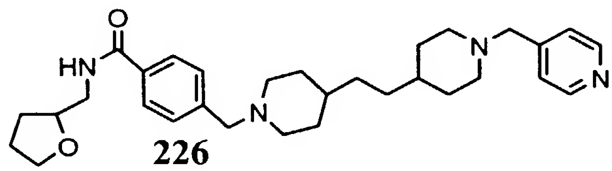

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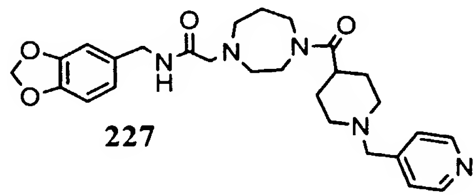

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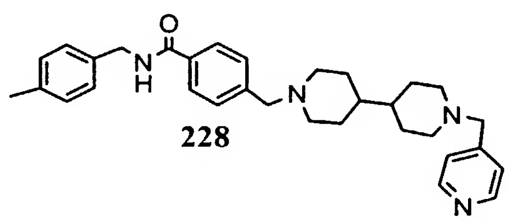

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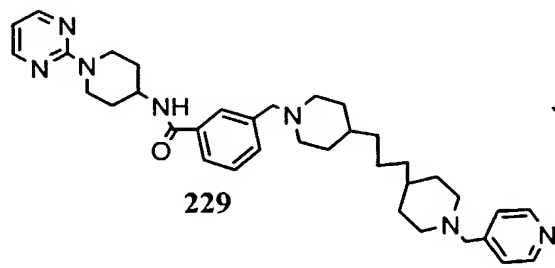

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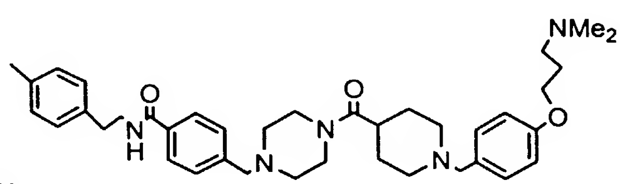

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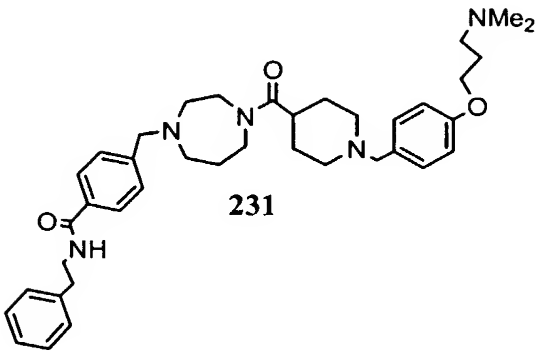

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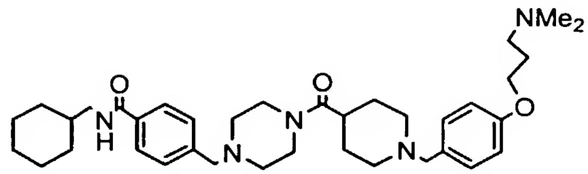

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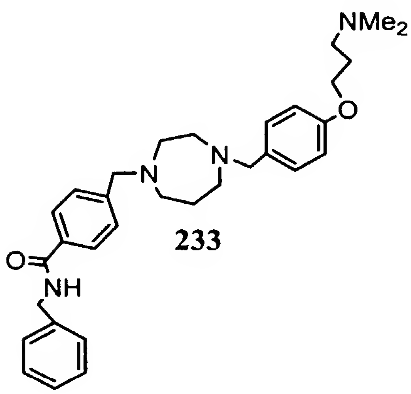

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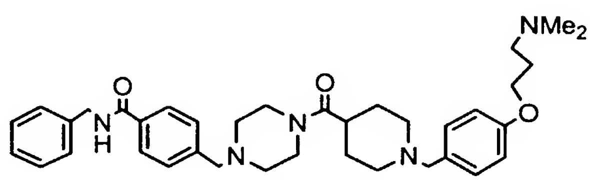

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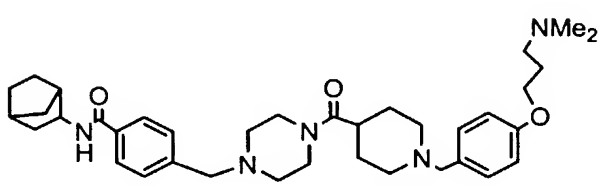

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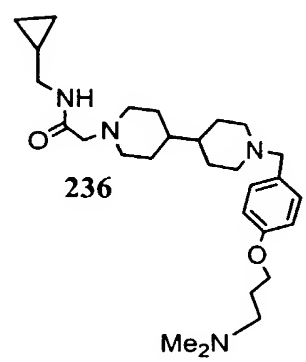

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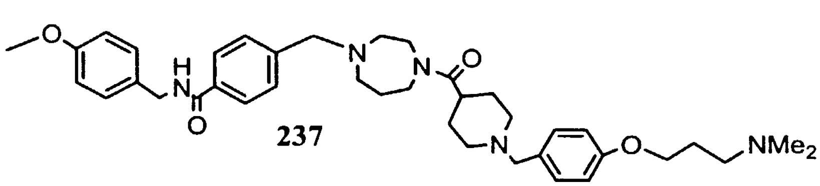

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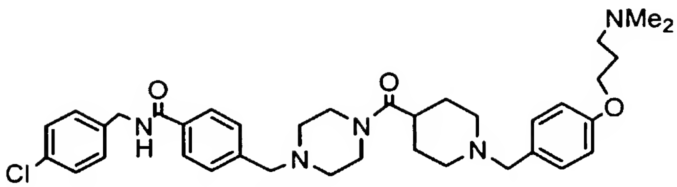

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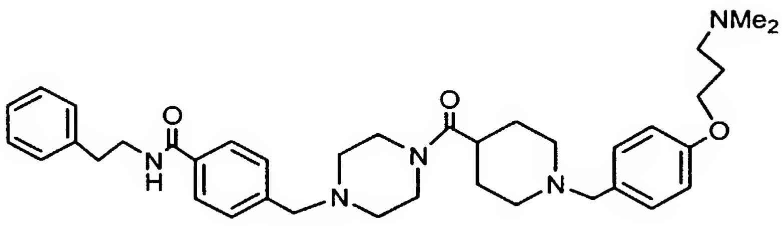

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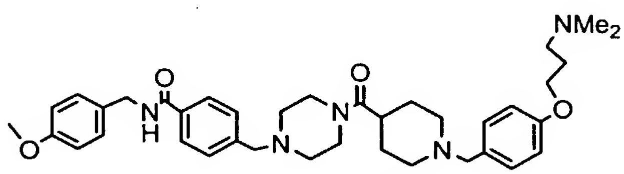

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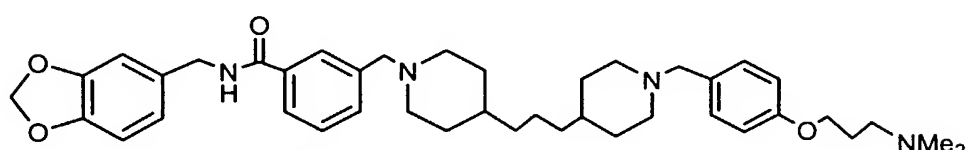

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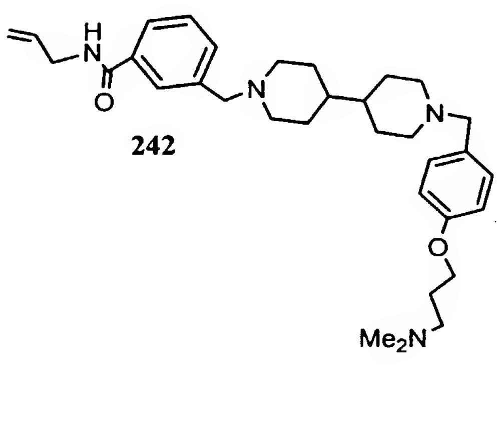

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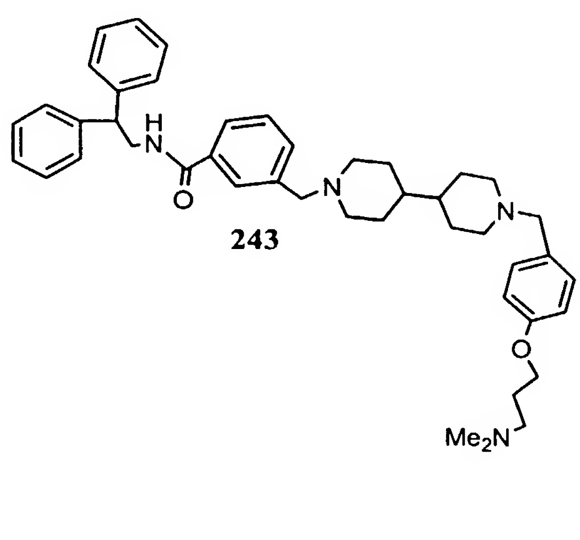

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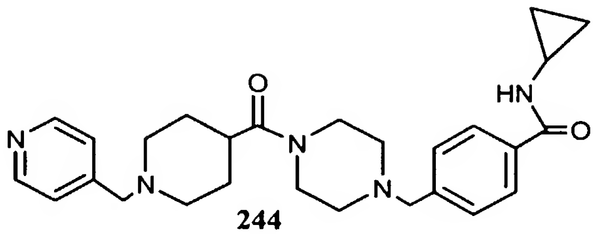

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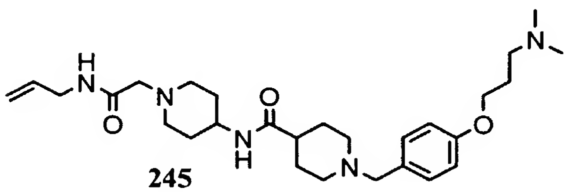

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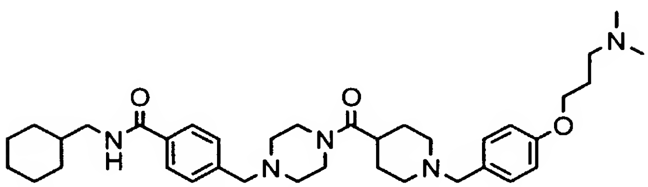

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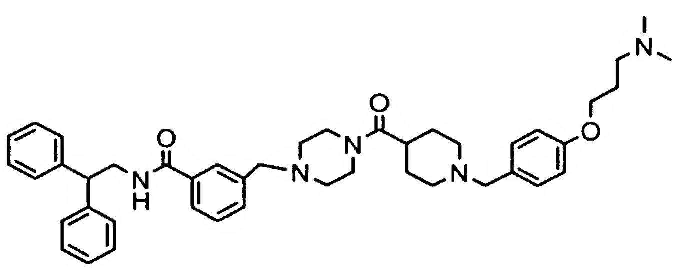

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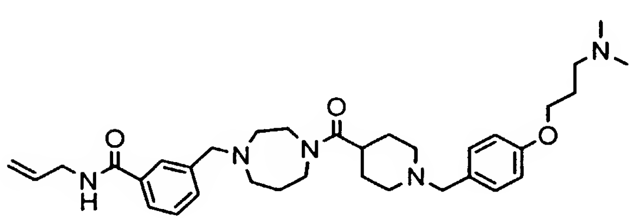

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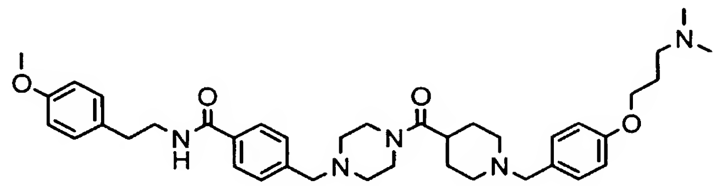

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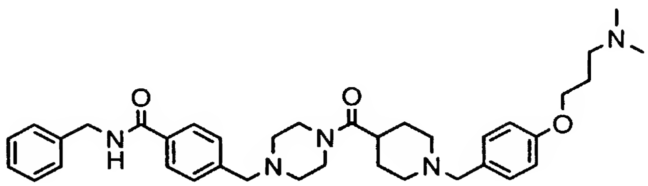

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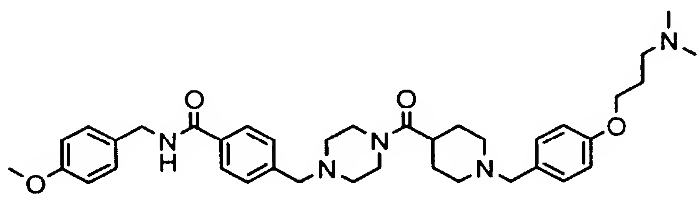

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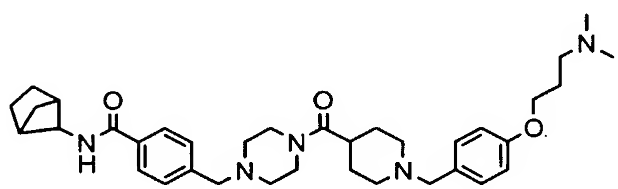

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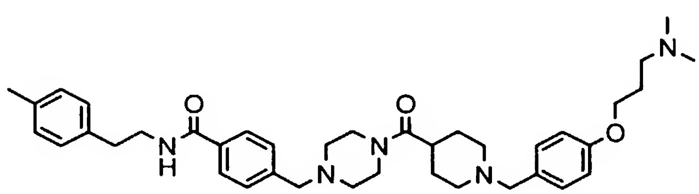

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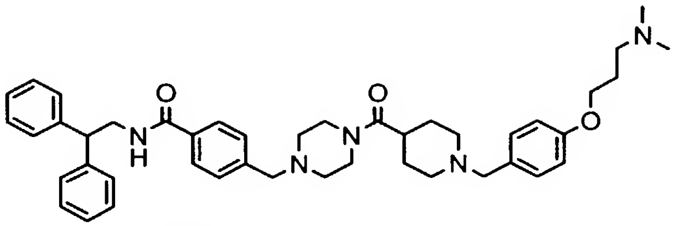

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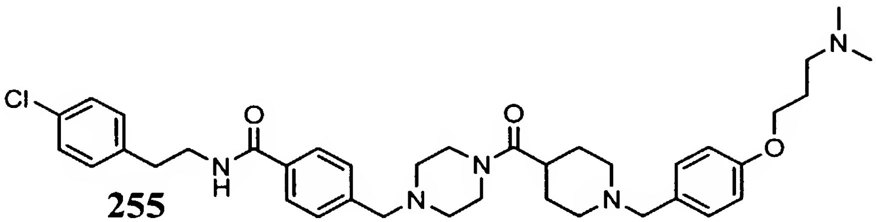

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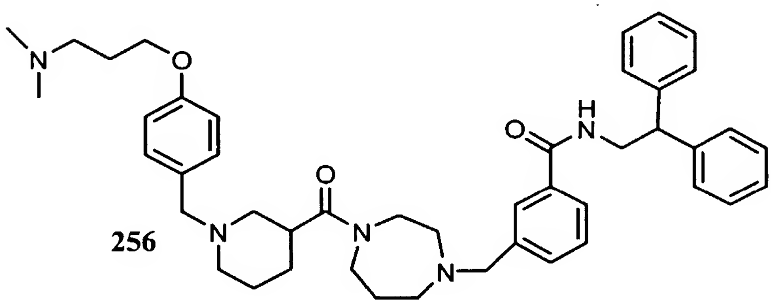

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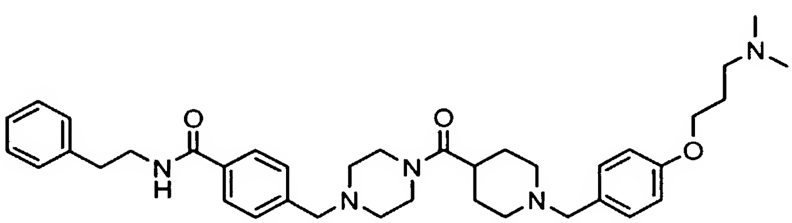

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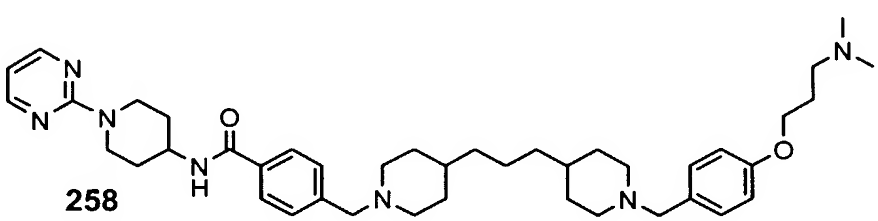

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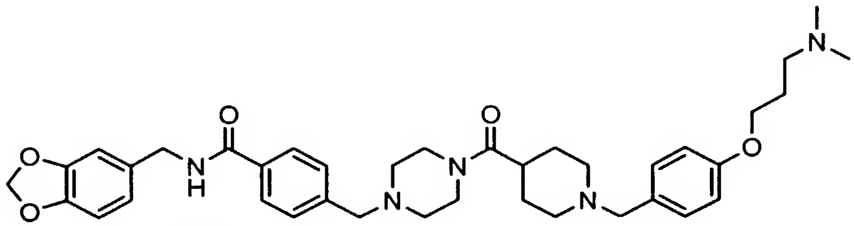

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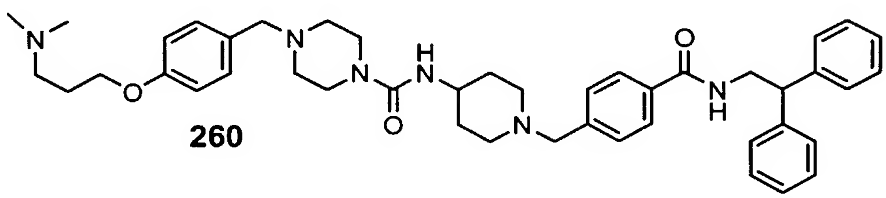

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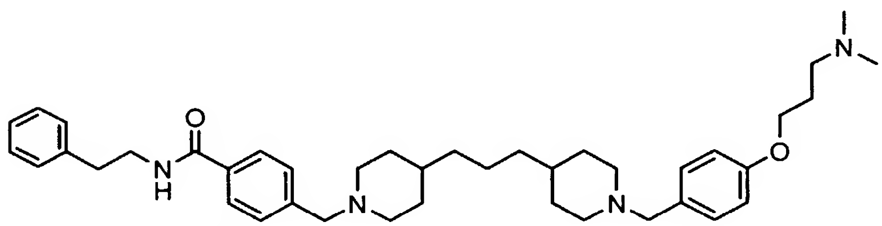

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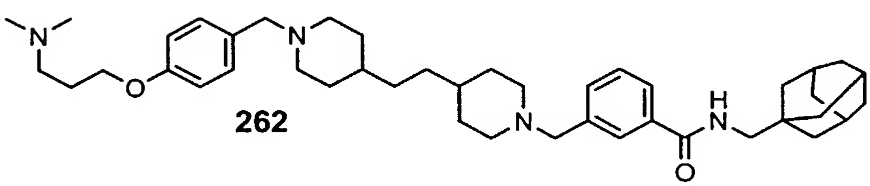

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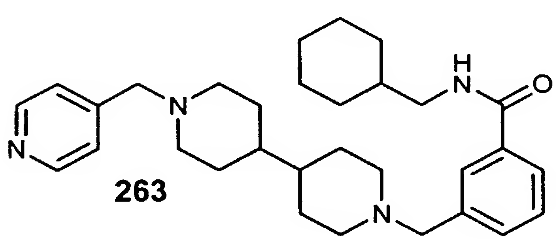

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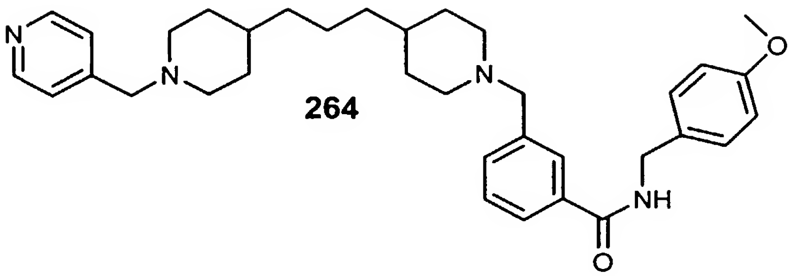

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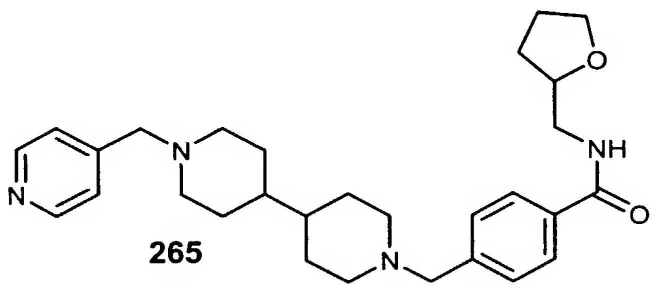

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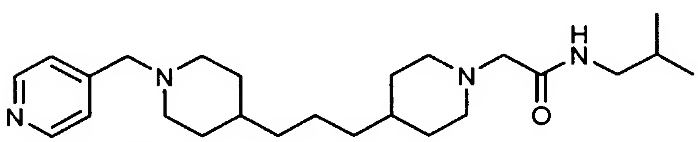

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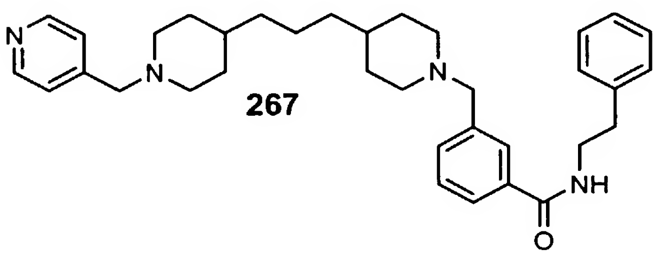

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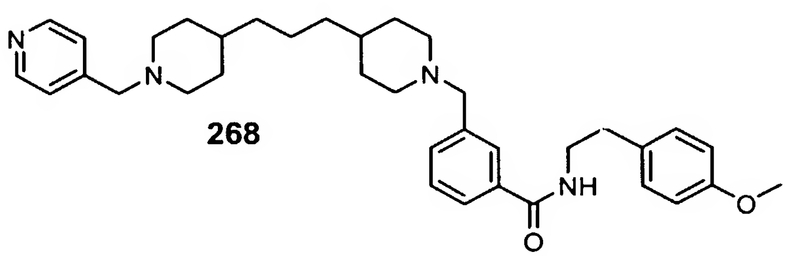

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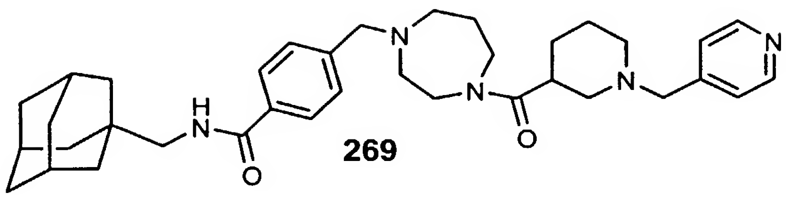

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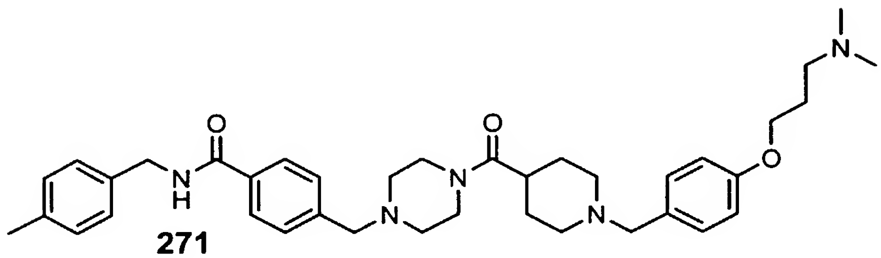

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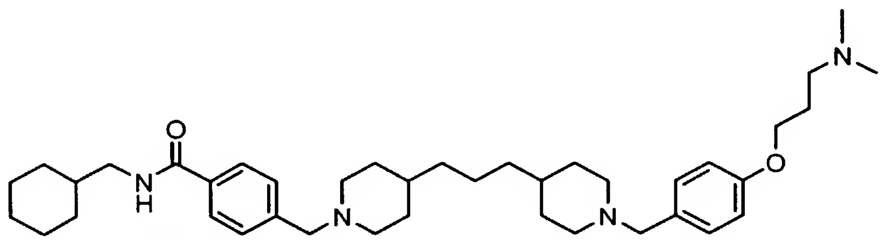
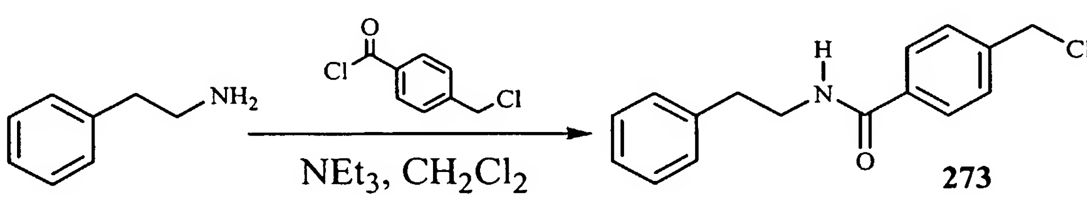


272

EXAMPLE 19

Compound **218** was prepared in solution in large quantity. The following is the procedure for the preparation of **218**, which serves as the general protocol for preparation of other analogs.



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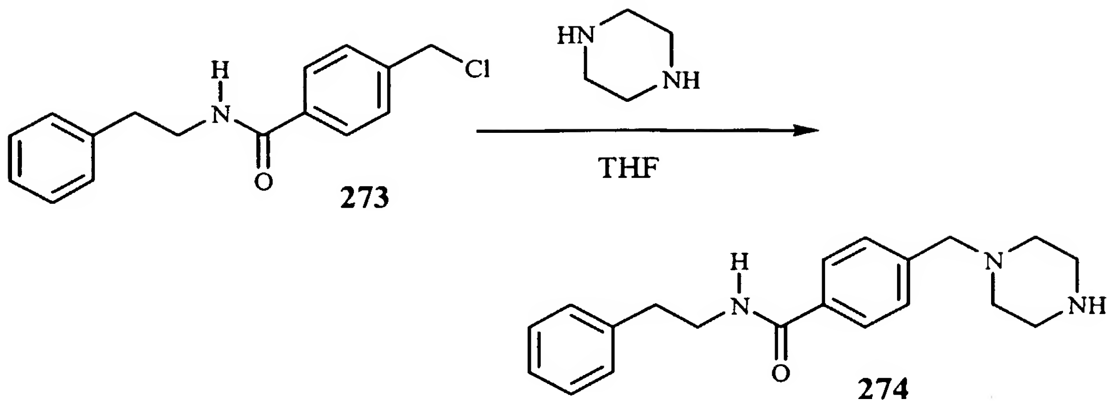
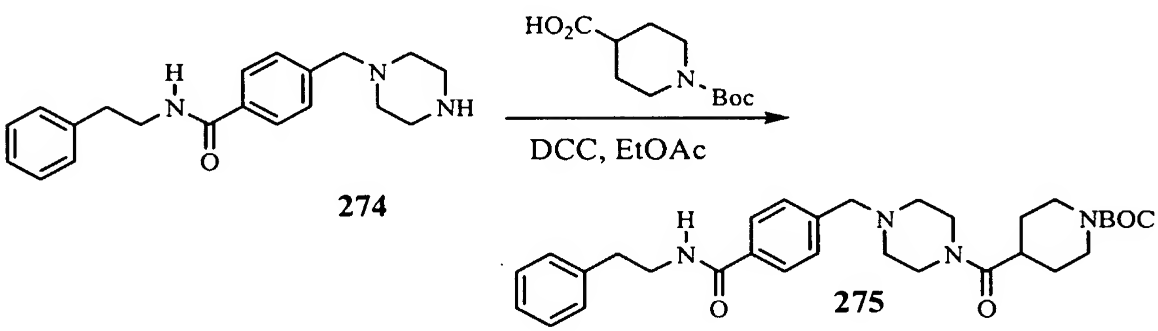
To a solution of Phenylethyl amine (120 mg, 1 mmole) and triethyl amine (200 mg, 2 mmole) in CH_2Cl_2 (10 mL) at 0 °C was added 4-(Chloromethyl)benzoyl chloride (230 mg, 1.2 mmole). After 30 min., the reaction mixture was poured into a separational funnel and washed with 1N HCl (10 mL), 1N NaOH (10 mL) and brine (10 mL). The organic layer was separated, dried over Na_2SO4, and filtered. The filtrate was concentrated to give compound **273** as colorless oil (260 mg, 95%).



273

274

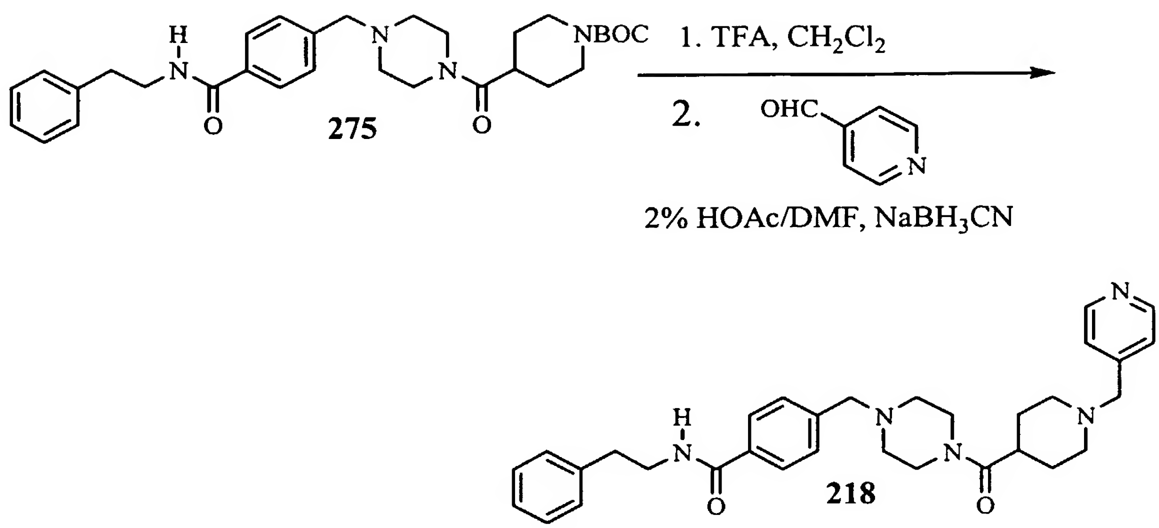
To a refluxed solution of compound **273** (260 mg, 0.95 mmole) in THF (10 mL) was added piperazine (430mg, 5 mmole). The mixture was under reflux for 1h and cooled to room temperature. Solvent was removed and the residue was dissolved in EtOAc (20 mL), which was washed with H_2O (2 x 10 mL), 1N NaOH (10 mL) and brine (10 mL). The organic layer was separated, dried over Na_2SO4, and filtered. The filtrate was concentrated to give compound **274** as a slightly yellow oil (290 mg, 95%).



274

275

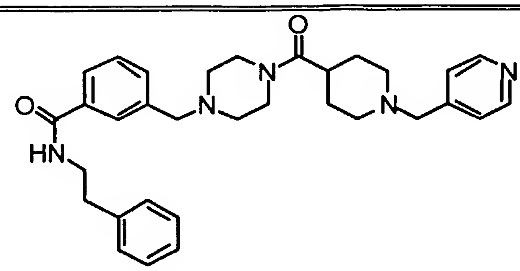
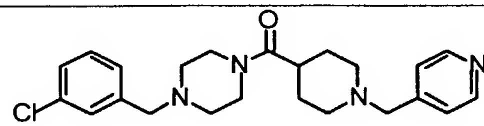
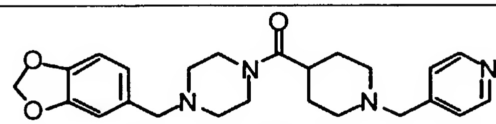
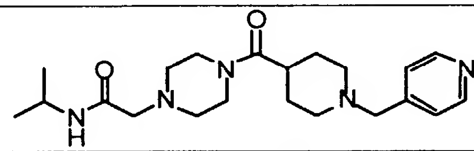
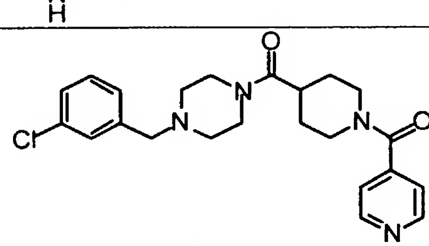
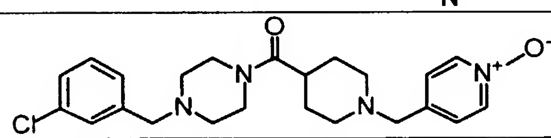
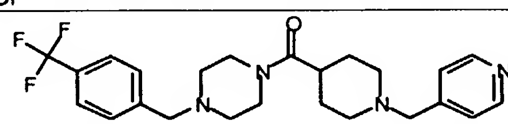
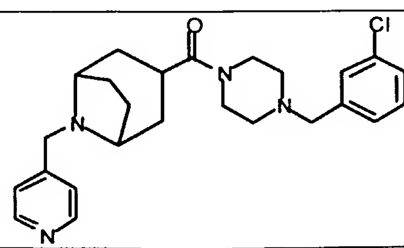
To a solution of Boc-isonipecotic acid (230 mg, 1 mmole) in EtOAc (10 mL) at 0° C was added DCC (206 mg, 1 mmole) followed by the addition of compound **274** (290 mg, 0.9 mmole) in EtOAc (5 mL). The reaction mixture was stirred at room temperature for 8h, and filtered. The filtrate was concentrated. Flash chromatography of the residue gave compound **275** as a colorless oil (390 mg, 80%)

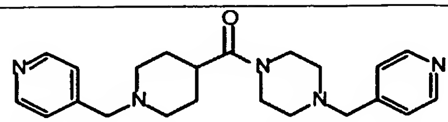
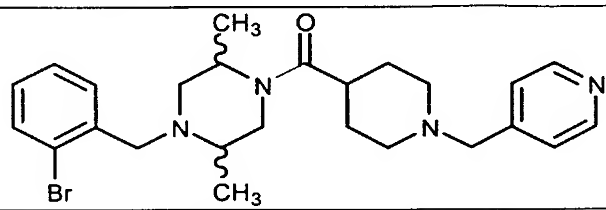
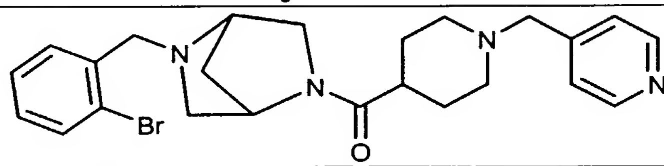
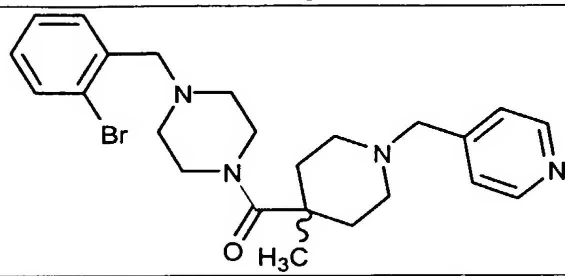
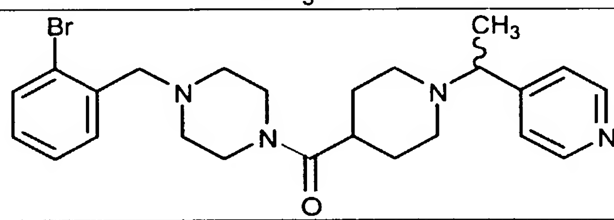
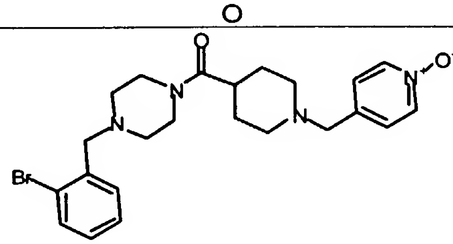
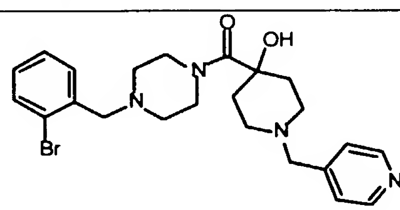
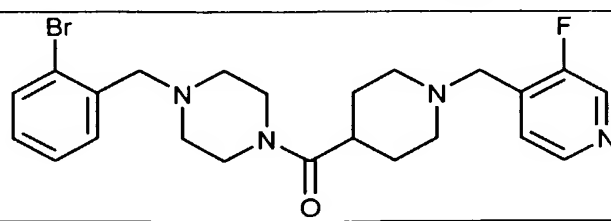


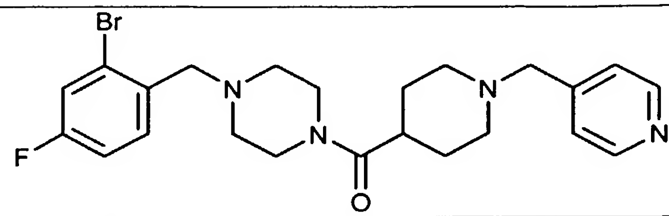
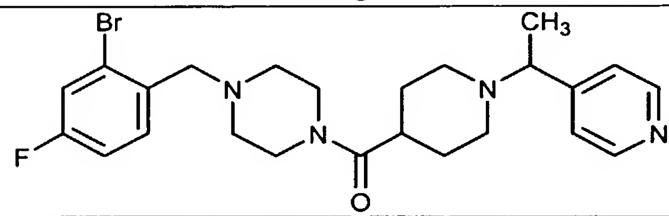
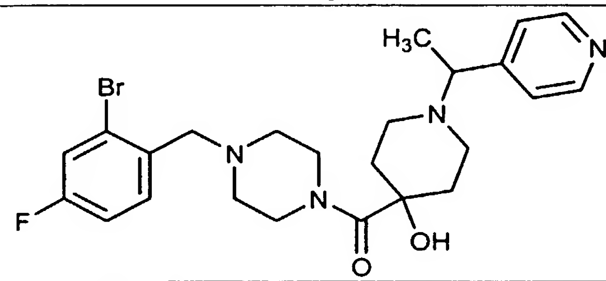
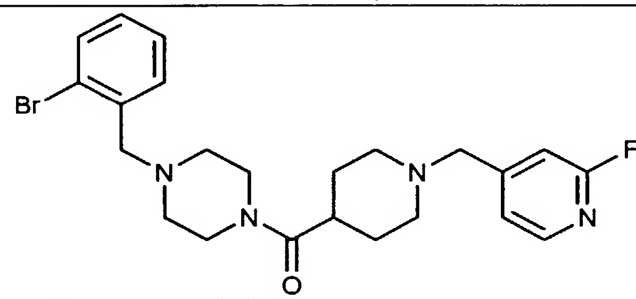
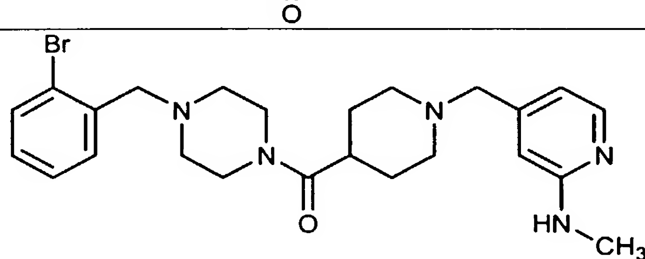
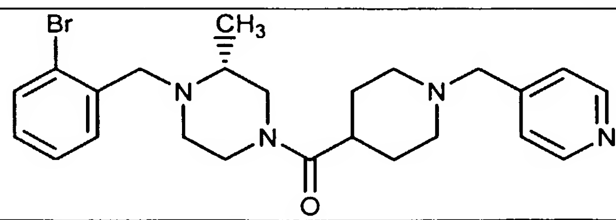
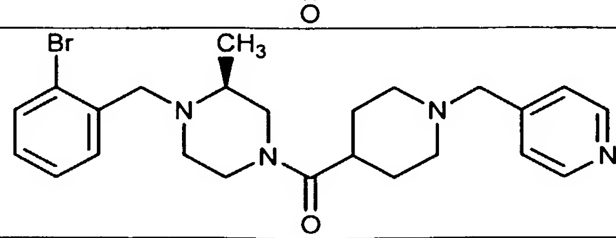
To a solution of compound **275** (270 mg, 0.5 mmole) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.5 mL). After 30 min., the mixture was concentrated, and the residue was dissolved in EtOAc (10 mL), which was washed with 1N NaOH (10 mL) and brine (10 mL). The organic layer was separated, dried over Na_2SO4 and filtered. The filtrate was concentrated and the residue was dissolved in DMF (5 mL). Acetic acid (0.2 mL), 4-pyridinecarboxaldehyde (64 mg, 0.6 mmole) and $NaBH_3CN$ (64 mg, 1 mmole) were added to the solution. The reaction mixture was kept at room temperature for 8h. EtOAc (15 mL) and H_2O (10 mL) were added to the mixture, and the mixtures were poured into a separational funnel. The organic layer was washed with H_2O (10 mL), 1N NaOH (10 mL) and brine (10 mL), separated and dried over Na_2SO4. After filtration, the filtrate was concentrated. Flash chromatography of the residue to give compound **218** as a white foam (132 mg, 50%).

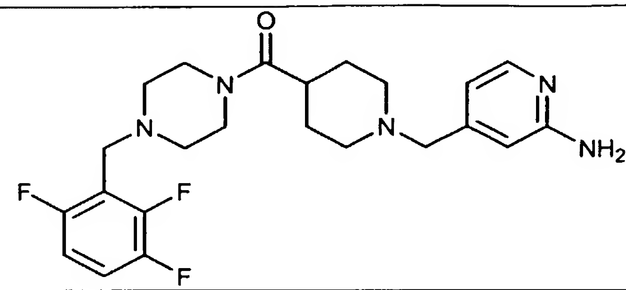
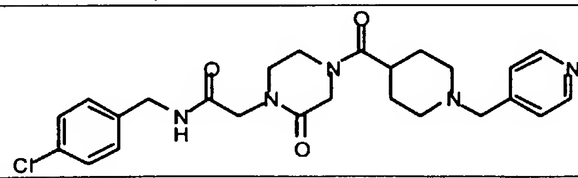
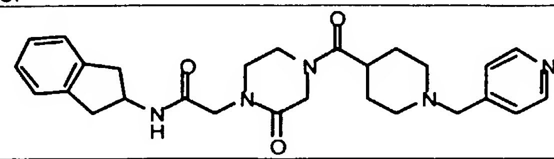
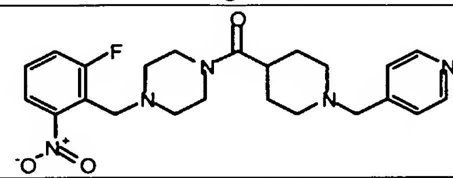
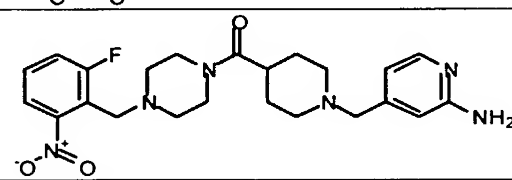
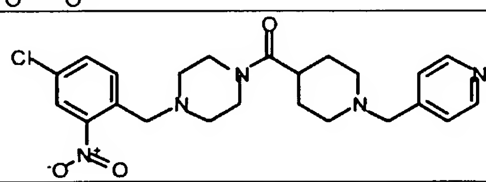
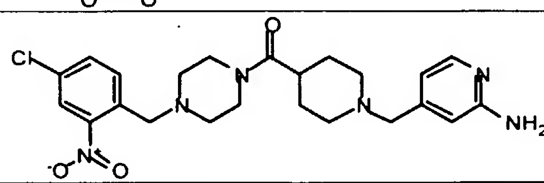
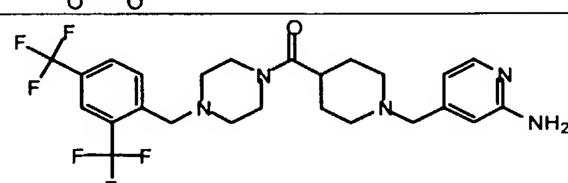
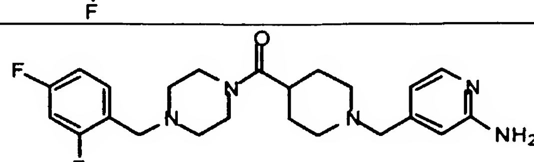
Following the procedure of Examples 1 to 17 the compounds in Table 5 were prepared.

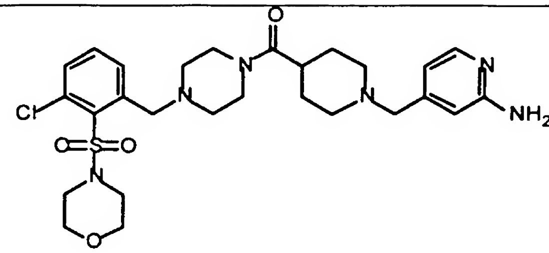
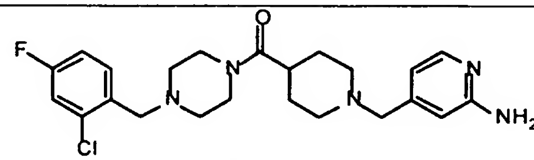
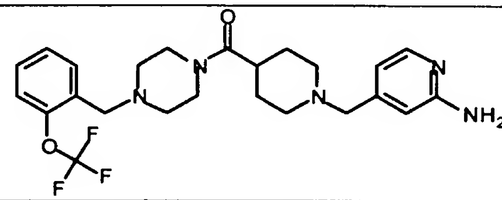
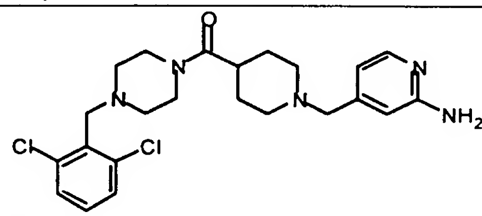
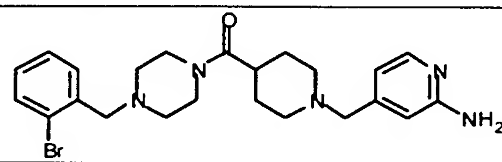
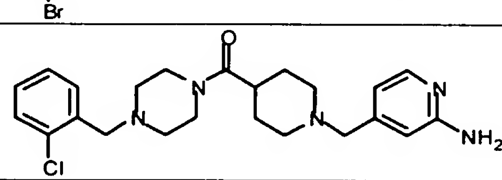
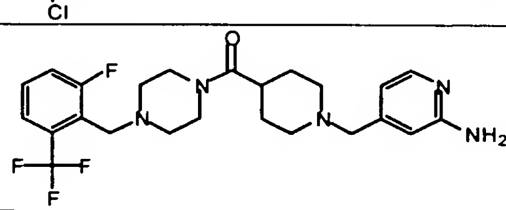
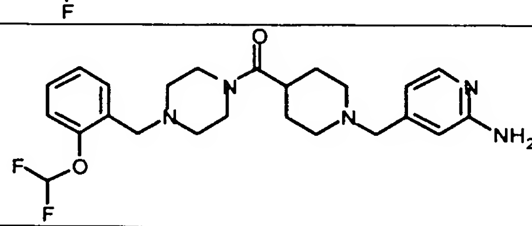
TABLE 5

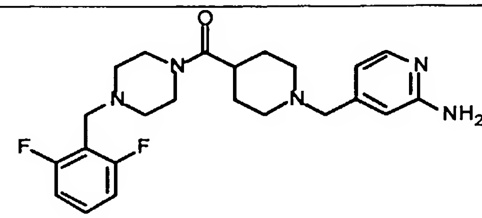
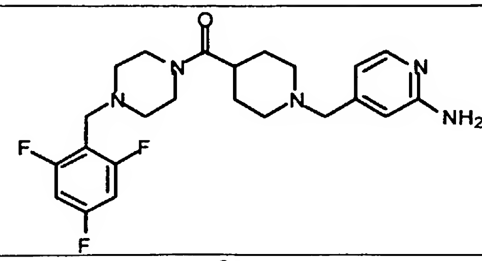
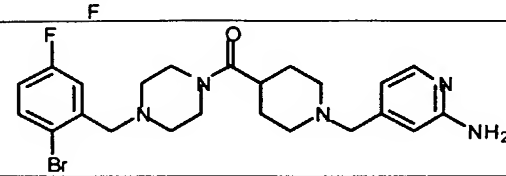
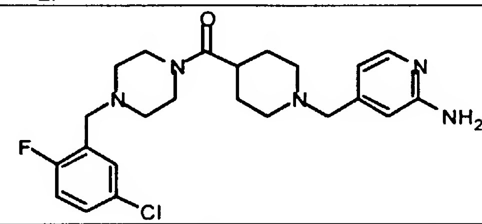
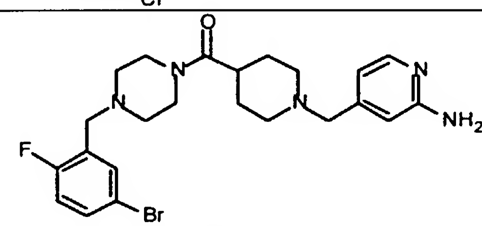
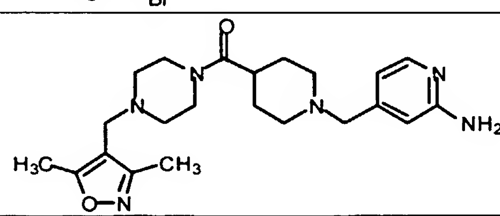
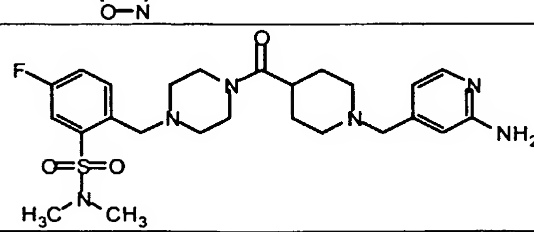
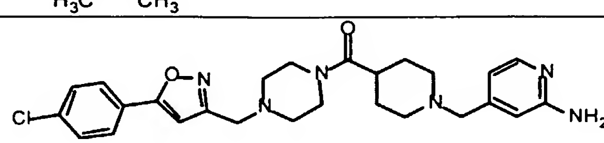
Compound No.	Structure
276	
277	
278	
279	
280	
281	
282	
284	

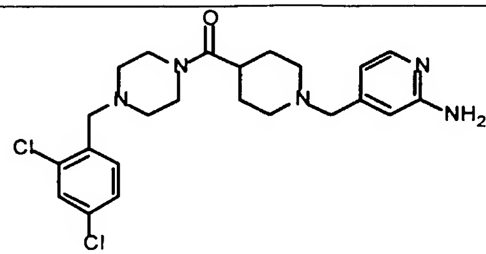
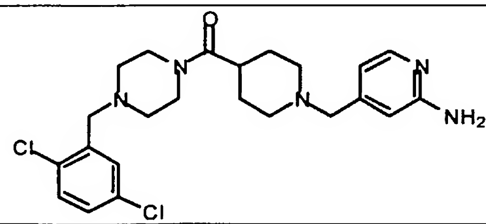
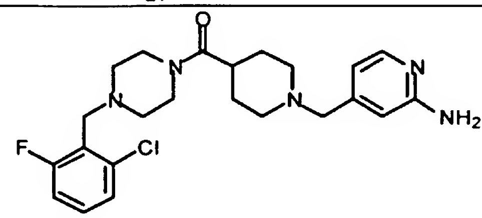
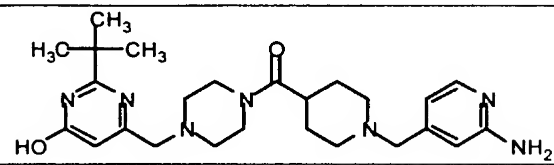
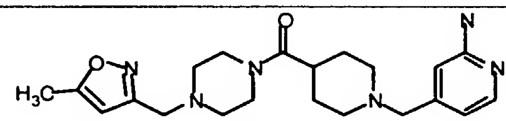
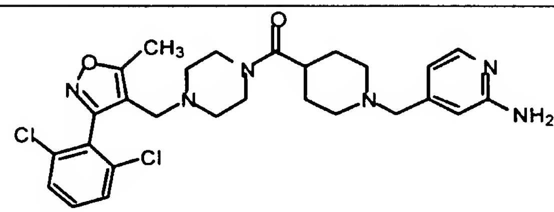
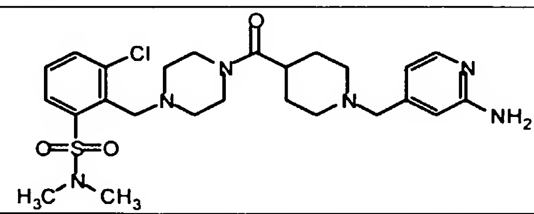
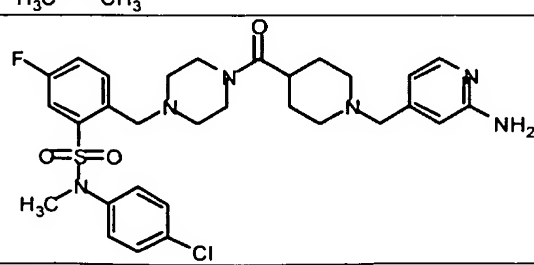
285	
287	
288	
289	
290	
291	
292	
293	

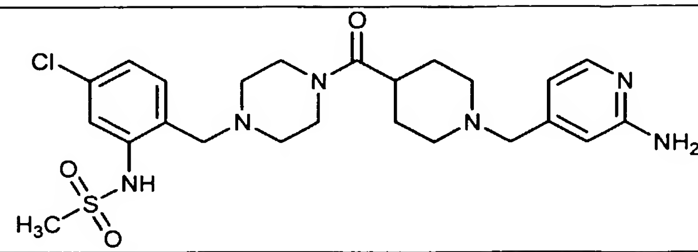
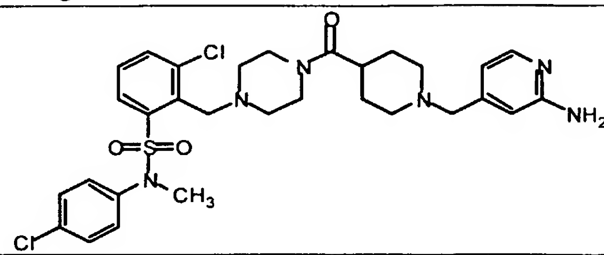
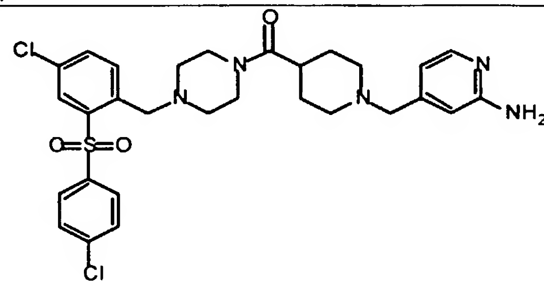
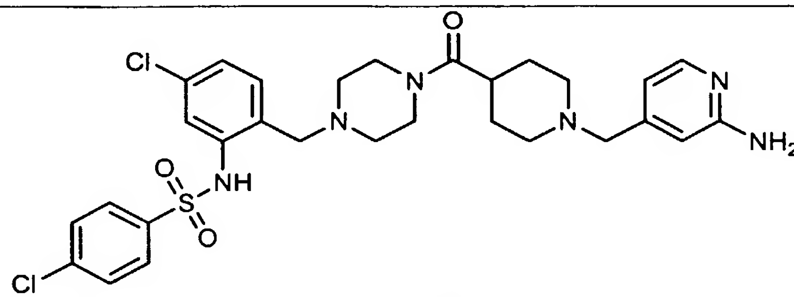
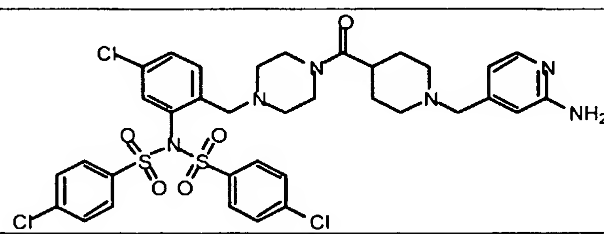
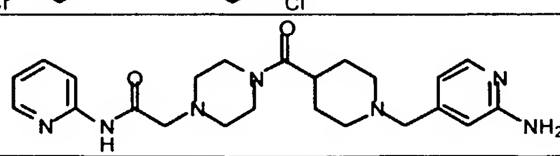
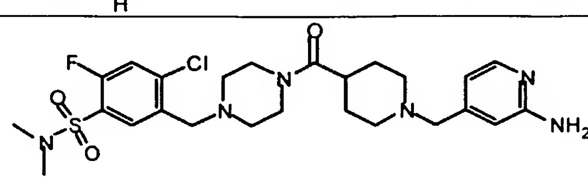
294	
295	
296	
297	
298	
299	
300	

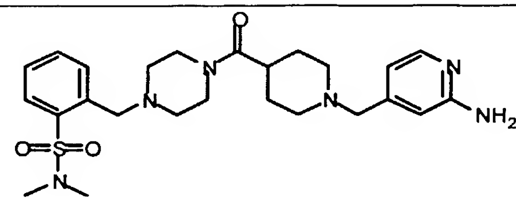
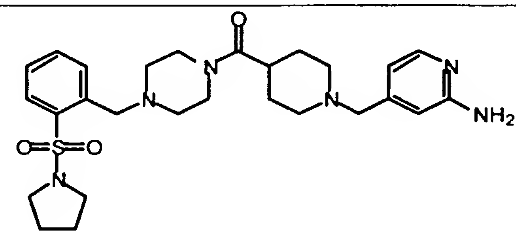
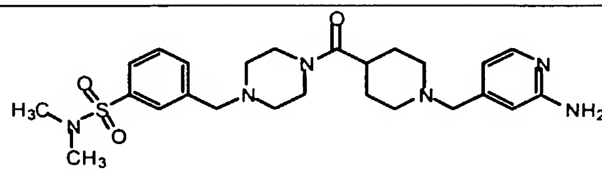
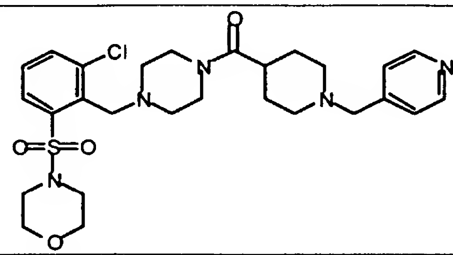
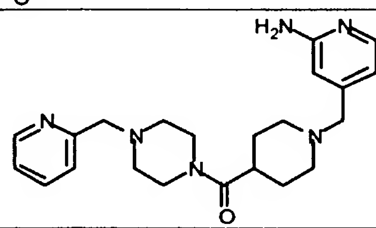
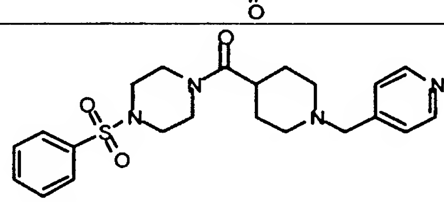
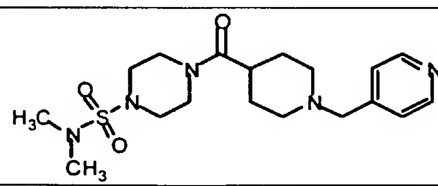
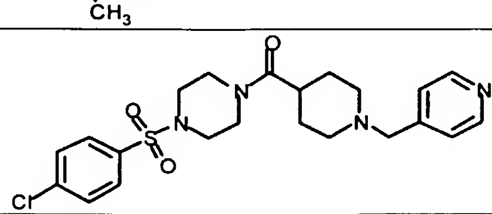
306	
309	
310	
311	
312	
313	
314	
315	
316	

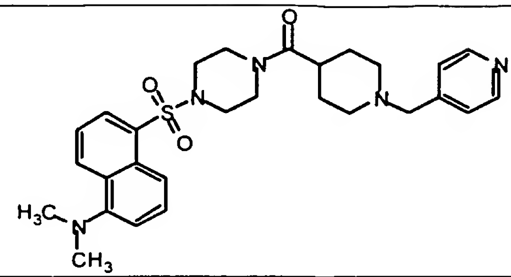
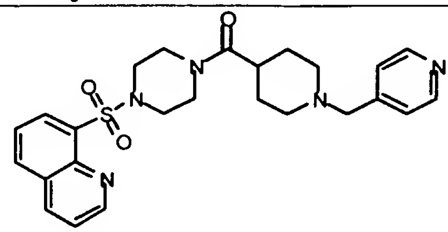
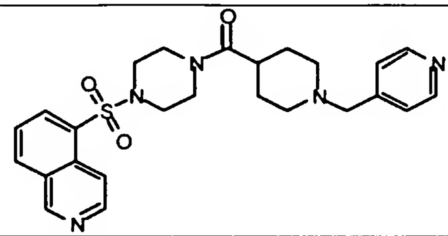
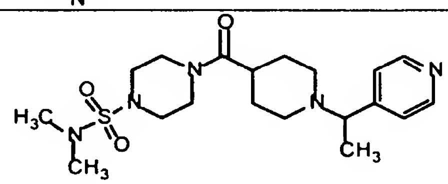
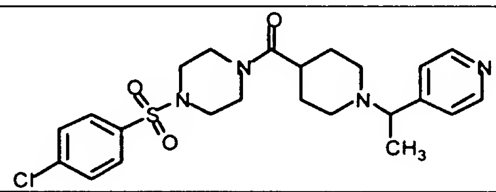
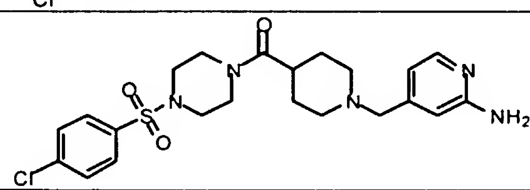
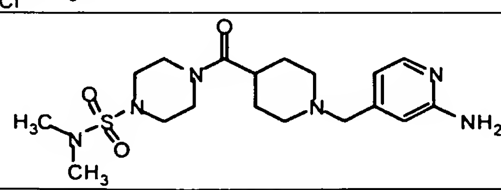
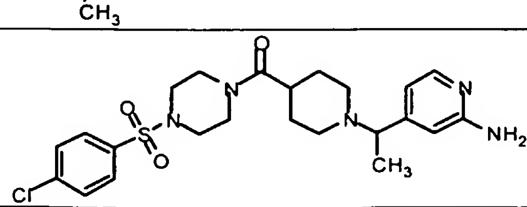
317	
318	
319	
321	
322	
323	
324	
325	

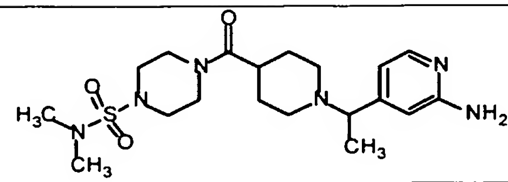
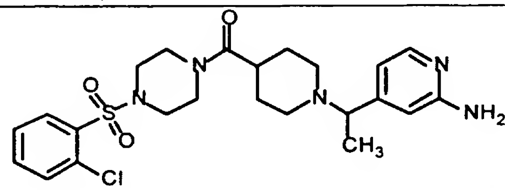
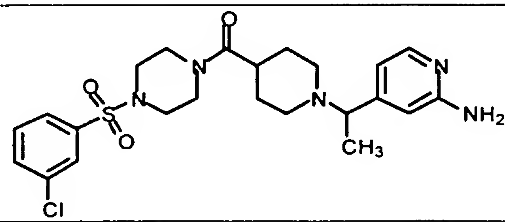
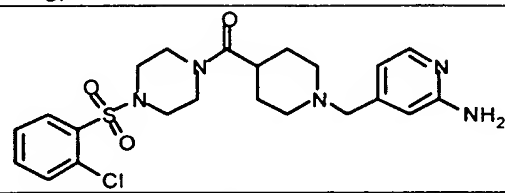
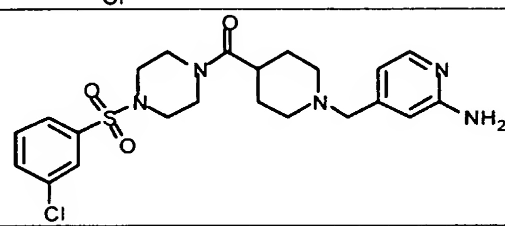
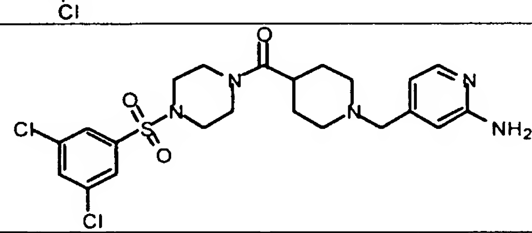
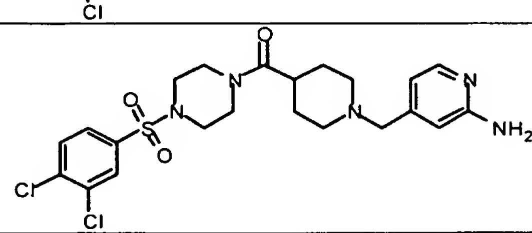
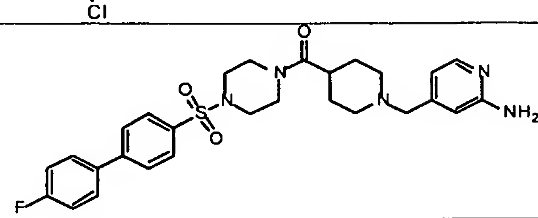
326	
327	
328	
329	
330	
331	
332	
333	

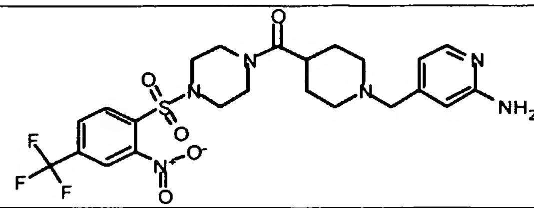
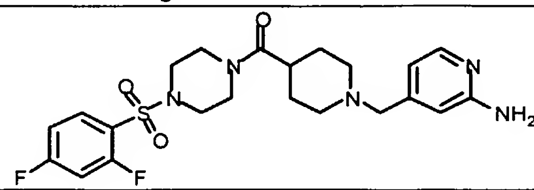
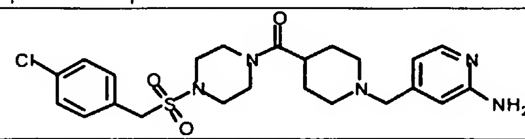
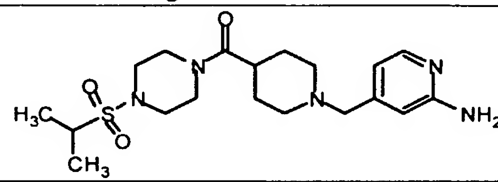
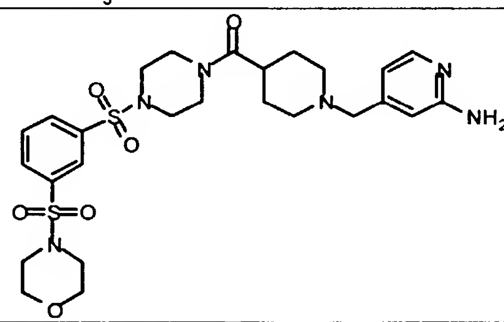
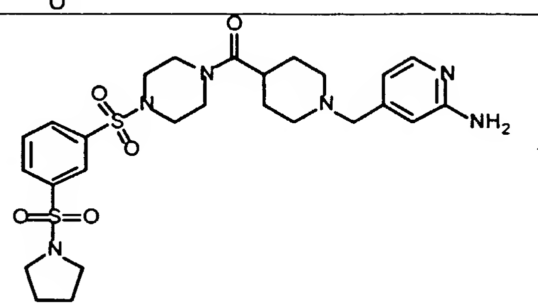
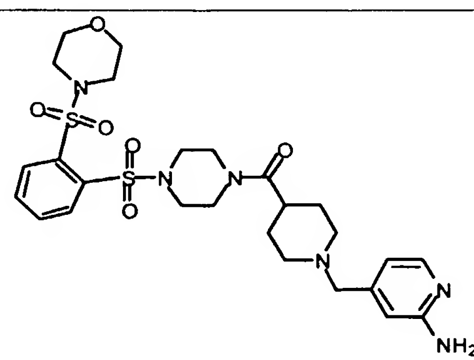
334	
335	
336	
338	
339	
340	
342	
343	

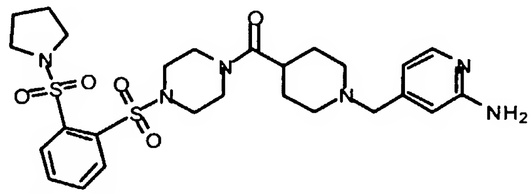
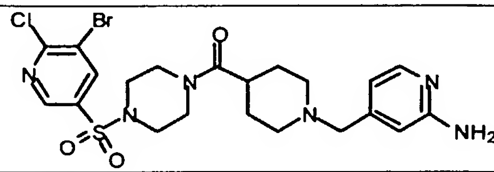
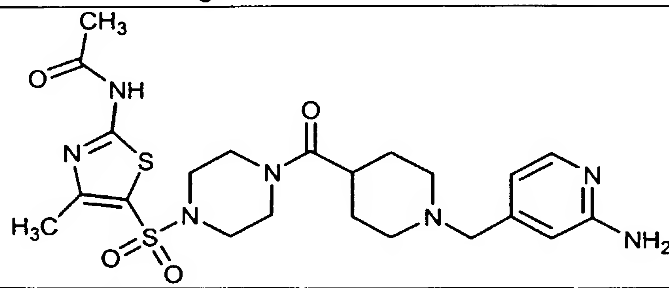
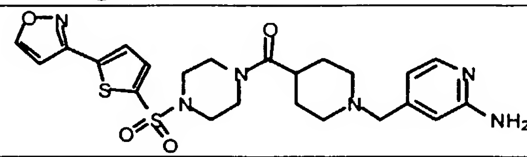
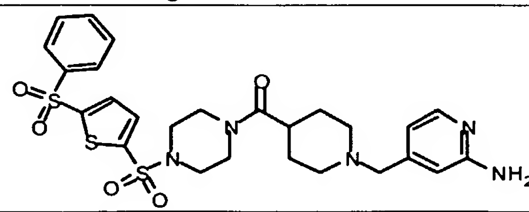
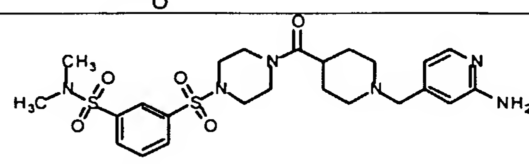
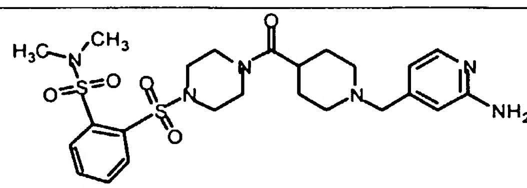
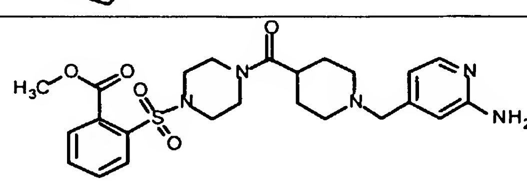
344	
345	
346	
347	
348	
349	
351	

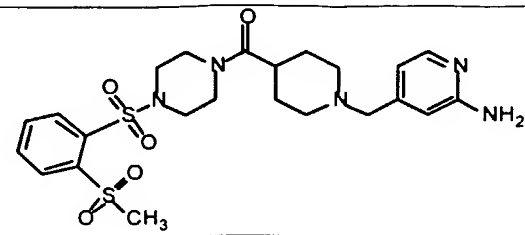
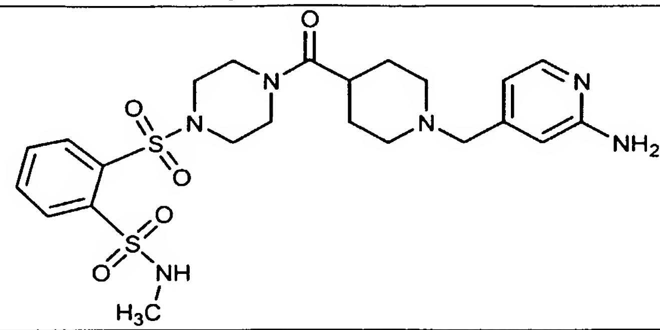
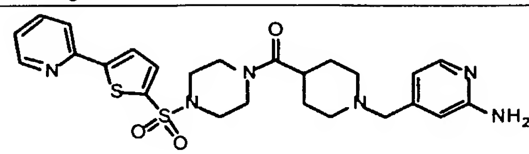
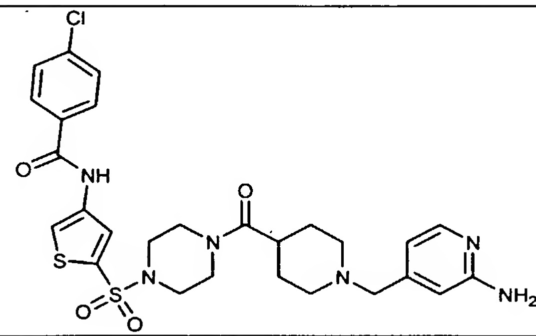
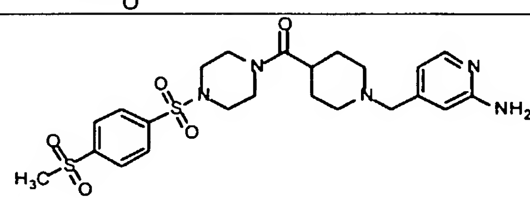
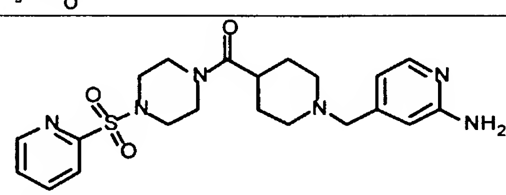
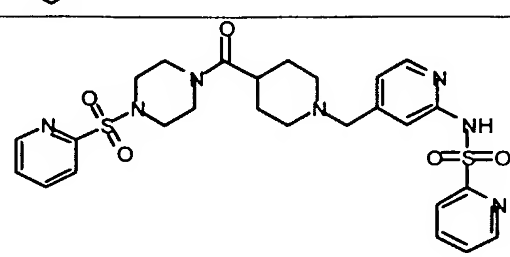
352	
353	
354	
355	
356	
357	
358	
359	

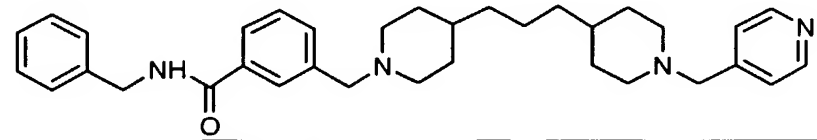
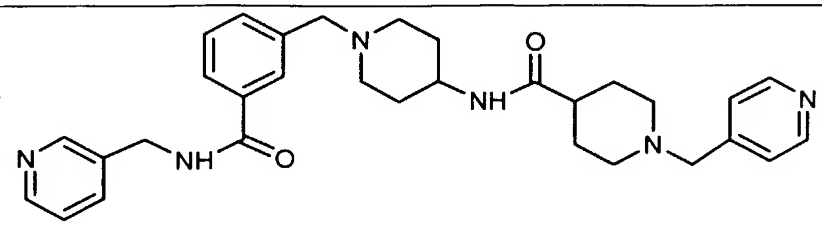
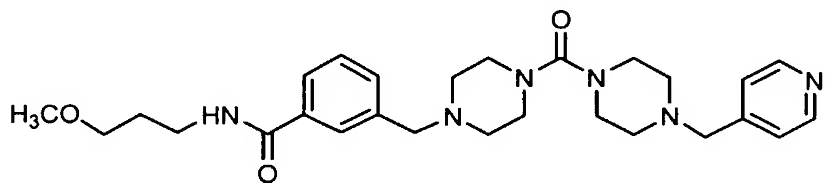
360	
361	
363	
364	
365	
366	
367	
368	

369	
370	
371	
374	
375	
376	
377	
380	

381	
382	
383	
387	
388	
389	
390	

392	
393	
394	
395	
396	
397	
398	
399	

400	
401	
402	
403	
404	
405	
406	

408	
409	
410	

General Procedure for H_3-Receptor Binding Assay

The source of the H_3 receptors in this experiment was guinea pig brain. The animals weighed 400-600 g. The brain tissue was homogenized with a solution of 50 mM Tris, pH 7.5. The final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1,000 x g for 10 min. in order to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to sediment the membranes, which were next washed three times in homogenization buffer (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was 2 μg/ml with 0.1% DMSO. Membranes were then added (400 μg of protein) to the reaction tubes. The reaction was started by the addition of 3 nM [^{3}H]R-α-methyl histamine (8.8 Ci/mmol) or 3 nM [^{3}H]N$^\alpha$-methyl histamine (80 Ci/mmol) and continued under incubation at 30°C for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitated by liquid scintillation spectrometry. All incubations were performed in duplicate and the standard error was always less than 10%. Compounds that

inhibited more than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K_i (nM).

Compounds 89 to 157, 159 to 168, 276 to 279, 282, 284, 285, 287 to 300, 306, 309 to 319, 321 to 336, 338 to 340, 342 to 349, 351 to 361, 363 to 371, 374 to 377, 380 to 383, 387 to 390, 392 to 406, and 408 to 410 had a K_i within the range of about 0.2 to about 600 nM.

Preferred Compounds 93, 276, 306, 317, 328, 331, 332, 333, 336, 343, 366, 367, 374 and 376 had a K_i within the range of about 0.2 to about 35 nM.

More preferred Compounds 306, 332, 333, 336, 366, 374 and 374 had a K_i within the range of about 2 to about 22 nM.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, PA.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or

emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 150 mg, preferably from about 1 mg to about 75 mg, more preferably from about 1 mg to about 50 mg, according to the particular application.

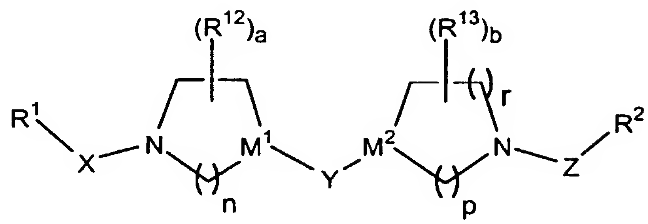
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 75 mg/day, in two to four divided doses.

While the present has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) R^1 is selected from:

(1) aryl;

(2) heteroaryl;

(3) heterocycloalkyl

(4) alkyl;

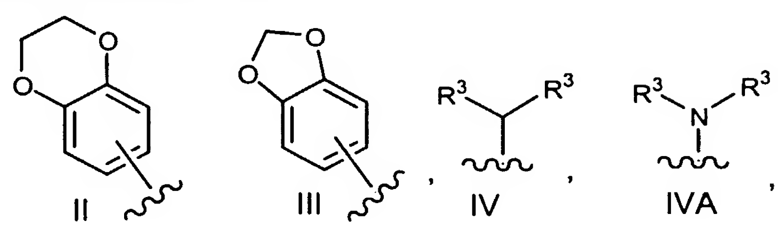
(5) $-C(O)N(R^{4B})_2$;

(6) cycloalkyl;

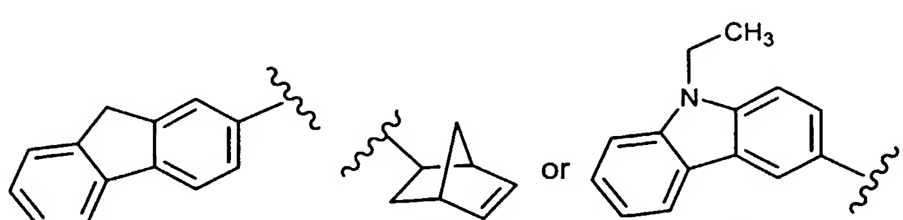
(7) arylalkyl;

(8) heteroarylheteroaryl; or

(9) a group selected from:



II, III, IV, IVA,



IVB, IVC, or IVD;

said aryl, heteroaryl, aryl portion of arylalkyl, phenyl ring of formula II, phenyl ring of formula III, phenyl rings of formula IVB, or phenyl rings of formula IVD are optionally substituted with 1 to 3 substituents independently selected from:

(1) halogen;
(2) hydroxyl;
(3) lower alkoxy;
(4) -Oaryl;
(5) $-SR^{22}$;
(6) $-CF_3$;
(7) $-OCF_3$;
(8) $-OCHF_2$;
(9) $-NR^4R^5$;
(10) phenyl;
(11) NO_2,
(12) $-CO_2R^4$;
(13) $-CON(R^4)_2$ wherein each R^4 is the same or different;
(14) $-S(O)_2R^{22}$;
(15) $-S(O)_2N(R^{20})_2$ wherein each R^{20} is the same or different;
(16) $-N(R^{24})S(O)_2R^{22}$;
(17) -CN;
(18) $-CH_2OH$;
(19) $-OCH_2CH_2OR^{22}$;
(20) alkyl;
(21) substituted phenyl wherein said phenyl has 1 to 3 substituents independently selected from alkyl, halogen, -CN, $-NO_2$, $-OCHF_2$, -Oalkyl;
(22) -Oalkylaryl wherein said aryl group is optionally substituted with 1 to 3 independently selected halogens; or
(23) phenyl;

(B) X is selected from alkyl or $-S(O)_2-$;

(C) Y represents
(1) a single bond; or
(2) Y is selected from –C(O)-, -C(S)-, $-(CH_2)_q$ -, or $–NR^4C(O)-$; with the provisos that:

(a) when M^1 is N, then Y is not $-NR^4C(O)-$; and

(b) when Y is a bond, then M^1 and M^2 are both carbon;

(D) M^1 and M^2 are independently selected from C or N;

(E) Z is selected from: C_1-C_6 alkyl, $-SO_2-$, -C(O)- or $-C(O)NR^4-$;

(F) R^2 is selected from:

(1) a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O, with the remaining ring atoms being carbon;

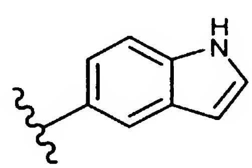
(2) a five-membered heteroaryl ring having 1 to 3 heteroatoms selected from nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; or

(3) an alkyl group;

(4) an aryl group wherein said substituted phenyl is substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-OCF_3$, $-CF_3$, -CN, $-NO_2$, $-NHC(O)CH_3$, or $-O(CH_2)_qN(R^{10A})_2$;

(5) $-N(R^{11A})_2$ wherein each R^{11A} is independently selected from: H, alkyl or aryl;

(6) a group of the formula:



; or

(7) a heteroarylheteroaryl group;

said five membered heteroaryl ring ((F)(2) above) or six-membered heteroaryl ring ((F)(1) above) is optionally substituted with 1 to 3 substituents selected from:

(a) halogen;

(b) hydroxyl;

(c) lower alkyl;

(d) lower alkoxy;

(e) $-CF_3$;

(f) $-NR^4R^5$;

(g) phenyl;

(h) $-NO_2$;

(i) $-C(O)N(R^4)_2$ (wherein each R^4 is the same or different);

(j) $-C(O)_2R^4$; or

(k) phenyl substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-OCF_3$, $-CF_3$, -CN, $-NO_2$ or $-O(CH_2)_qN(R^{10A})_2$;

(G) R^3 is is selected from:

(1) aryl;

(2) heteroaryl;

(3) heterocycloalkyl

(4) alkyl; or

(5) cycloalkyl;

wherein said aryl or heteroaryl R^3 groups is optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen;

(b) hydroxyl;

(c) lower alkoxy;

(d) -Oaryl;

(e) $-SR^{22}$;

(f) $-CF_3$;

(g) $-OCF_3$;

(h) $-OCHF_2$;

(i) $-NR^4R^5$;

(j) phenyl;

(k) $-NO_2$,

(l) $-CO_2R^4$;

(m) $-CON(R^4)_2$ wherein each R^4 is the same or different;

(n) $-S(O)_2R^{22}$;

(o) $-S(O)_2N(R^{20})_2$ wherein each R^{20} is the same or different;

(p) $-N(R^{24})S(O)_2R^{22}$;

(q) -CN;

(r) $-CH_2OH$;

(s) $-OCH_2CH_2OR^{22}$; or

(t) alkyl;

(H) R^4 is selected from:

(1) hydrogen;

(2) C_1-C_6 alkyl;

(3) cycloalkyl;

(4) cycloalkylalkyl;

(5) heterocycloalkylalky;

(6) bridged bicyclic cycloalkyl ring;

(7) aryl having a fused heterocycloalkyl ring bound to said aryl ring;

(8) aryl;

(9) arylalkyl;

(10) alkylaryl;

(11) $-(CH_2)_dCH(R^{12A})_2$ wherein d is 1 to 3, and each R^{12A} is independently selected from phenyl or substituted phenyl, said substituted phenyl being substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-OCF_3$, $-CF_3$, -CN, or $-NO_2$;

(12) heterocycloalkylheteroaryl; or

(13) -(C_1 to C_6)alkylene-O-R^{22};

wherein the aryl R^4 group, the aryl portion of the arylalkyl R^4 group, or the aryl portion of the alkylaryl R^4 group is optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen;

(b) hydroxyl;

(c) lower alkyl;

(d) lower alkoxy;

(e) $-CF_3$;

(f) $-N(R^{20})(R^{24})$,

(g) phenyl;

(h) $-NO_2$;

(i) $-C(O)N(R^{20})_2$ (wherein each R^{20} is the same or different),

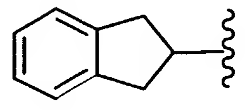
(j) $-C(O)R^{22}$;

(i) $-(CH_2)_k$-cycloalkyl;

(j) $-(CH_2)_q$-aryl; or

(k) $-(CH_2)_m-OR^{22}$;

(I) each R^{4B} is independently selected from: H, heteroaryl, alkyl, alkenyl, a group of the formula



arylalkyl, or arylalkyl wherein the aryl moiety is substitued with 1-3 substituents independently selected from: halogen;

(J) R^5 is selected from: hydrogen, C_1-C_6 alkyl, -C(O)R^{20}, -C(O)$_2R^{20}$, –C(O)N(R^{20})$_2$ (wherein each R^{20} is the same or different);

(K) each R^{10A} is independently selected from H or C_1 to C_6 alkyl, or each R^{10A}, taken together with the nitrogen atom to which they are bound, forms a 4 to 7 membered heterocycloalkyl ring;

(L) R^{12} is

(1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R^{12} is hydroxy or fluoro then R^{12} is not bound to a carbon adjacent to a nitrogen; or

(2) R^{12} forms an alkyl bridge from one ring carbon to another ring carbon;

(M) R^{13} is

(1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R^{13} is hydroxy or fluoro then R^{13} is not bound to a carbon adjacent to a nitrogen; or

(2) R^{13} forms an alkyl bridge from one ring carbon to another ring carbon;

(N) R^{20} is selected from hydrogen, alkyl, or aryl, wherein said aryl group is optionally substituted with from 1 to 3 groups independently selected from: halogen, -CF_3, -OCF_3, hydroxyl, or methoxy; or when two R^{20} groups are present, said two R^{20} groups taken together with the nitrogen to which they are bound form a five or six membered heterocyclic ring;

(O) R^{22} is selected from: heterocycloalkyl, alkyl or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, -CF_3, -OCF_3, hydroxyl, or methoxy;

(P) R^{24} is selected from: hydrogen, alkyl, $-SO_2R^{22}$, or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;

(Q) a is 0 to 2;

(R) b is 0 to 2;

(S) k is 1 to 5;

(T) m is 2 to 5;

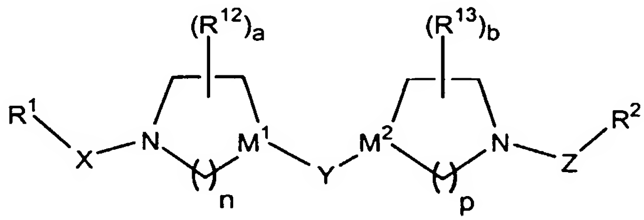
(U) n is 1, 2 or 3 with the proviso that when M^1 is N, then n is not 1;

(V) p is 1, 2 or 3 with the proviso that when M^2 is N, then p is not 1;

(W) q is 1 to 5; and

(X) r is 1, 2, or 3 with the proviso that when r is 2 or 3, then M^2 is C and p is 1.

2. The compound of Claim 1 having the formula:



(V)

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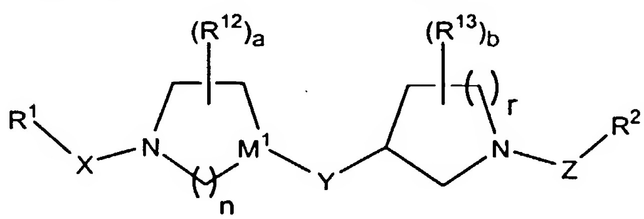
3. The compound of Claim 1 havng the formula:



(VI)

.

4. The compound of Claim 1 wherein R^1 is selected from:

(1) substituted aryl;

(2) substituted heteroaryl; or

(3) formula IVA wherein each R^3 is independently selected.

5. The compound of Claim 4 wherein R^1 is selected from:

(1) substituted phenyl;

(2) substituted isoxazolyl; or

(3) $-N(CH_3)_2$.

6. The compound of Claim 5 wherein R^1 is selected from:

(1) substituted phenyl wherein said phenyl group has 1 to 3 groups selected independently selected from:

(a) $-C(O)N(R^4)_2$;

(b) halo;

(c) $-S(O)_2R^{22}$;

(d) $-OCF_3$;

(e) $-OCHF_2$; or

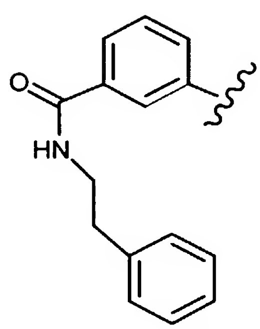
(f) $-S(O)_2N(R^{20})_2$; or

(2) substituted isoxazolyl wherein said isoxazolyl group has 1 or 2 substituents independently selected from:

(a) alkyl; or

(b) substituted phenyl.

7. The compound of Claim 1 wherein R^1 is selected from: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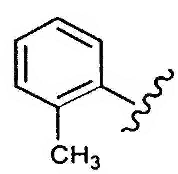
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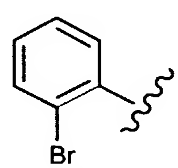
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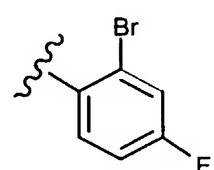
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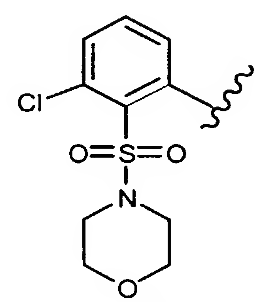
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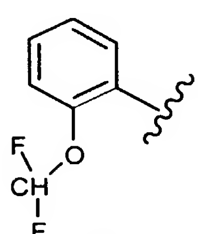
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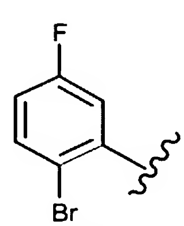
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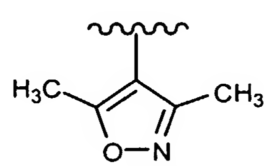
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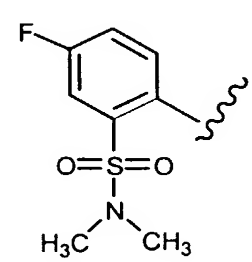
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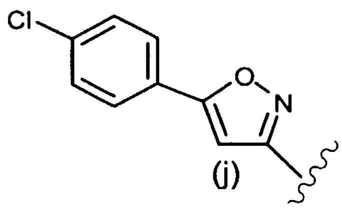
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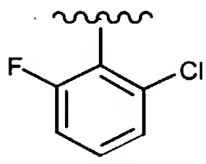
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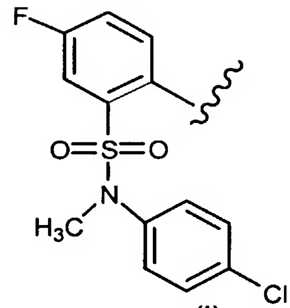
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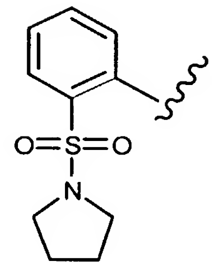
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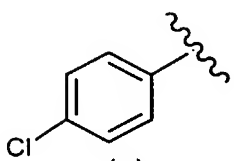
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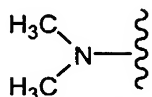
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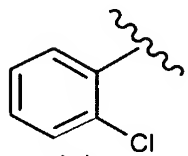
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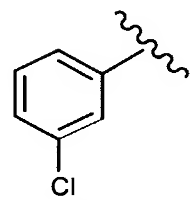
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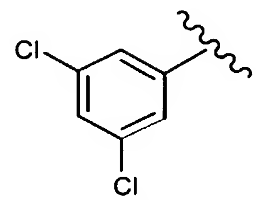
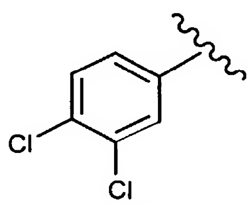

(r) , or

(s) .

8. The compound of Claim 1 wherein X is $-CH_2-$ or $-SO_2-$.

9. The compound of Claim 1 wherein M^1 is nitrogen.

10. The compound of Claim 9 wherein n is 2.

11. The compound of Claim 1 wherein Y is $-C(O)-$.

12. The compound of Claim 1 wherein M^2 is C.

13. The compound of Claim 12 wherein p is 2.

14. The compound of Claim 1 wherein r is 1.

15. The compound of Claim 1 wherein Z is an alkyl group.

16. The compound of Claim 15 wherein Z is

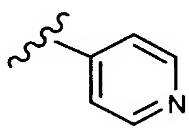
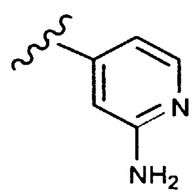
$$-CH_2- \quad \text{or} \quad -\overset{\displaystyle CH_3}{\overset{|}{C}}H- \; .$$

17. The compound of Claim 1 wherein R^2 is a six membered heteroaryl ring or a substituted six membered heteroaryl ring.

18. The compound of Claim 17 wherein R^2 is pyridyl or substituted pyridyl.

19. The compound of Claim 18 wherein said substituted pyridyl is substituted with $-NH_2$.

20. The compound of Claim 18 wherein R^2 is selected from:

 or  .

21. The compound of Claim 1 wherein a is 0 and b is 0.

22. The compound of Claim 1 wherein:
(A) R^1 is selected from:
(1) substituted aryl;
(2) substituted heteroaryl; or
(3) formula IVA wherein each R^3 is independently selected.
(B) X is $-CH_2-$ or $-SO_2-$;
(C) M^1 is nitrogen;
(D) n is 2;
(E) Y is $-C(O)-$;

(F) M^2 is C;

(G) p is 2;

(H) r is 1;

(I) Z is an alkyl group;

(J) R^2 is a six membered heteroaryl ring or a substituted six membered heteroaryl ring;

(K) a is 0; and

(L) b is 0.

23. The compound of Claim 22 wherein R^1 is selected from:

(1) substituted phenyl;

(2) substituted isoxazolyl; or

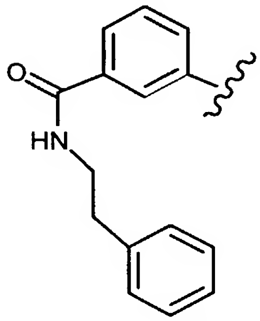
(3) $-N(CH_3)_2$.

24. The compound of Claim 23 wherein R^2 is pyridyl or substituted pyridyl.

25. The compound of Claim 24 wherein Z is selected from:

$$-CH_2- \quad \text{or} \quad -\overset{\displaystyle CH_3}{\overset{|}{C}}H- \; .$$

26. The compound of Claim 25 wherein R^1 is selected from: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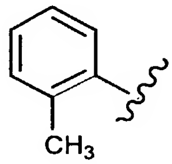
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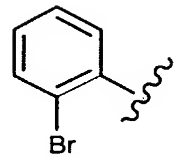
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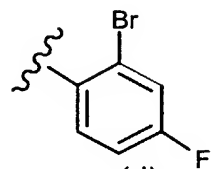
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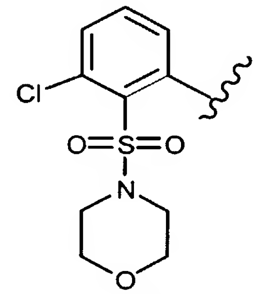
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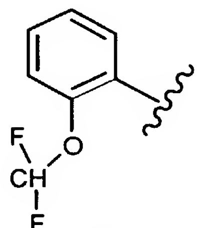
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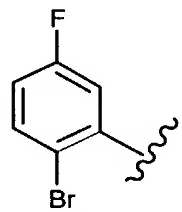
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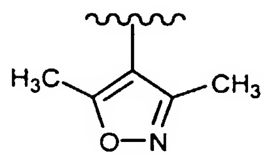
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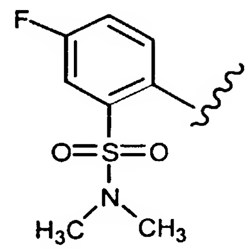
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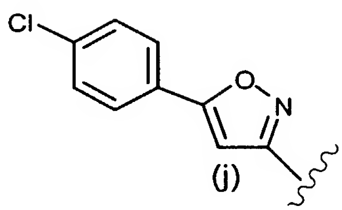
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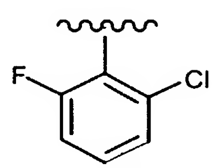
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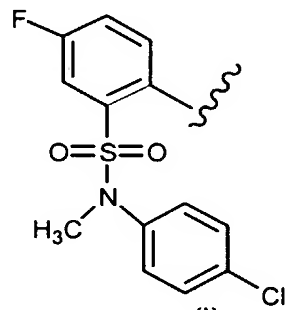
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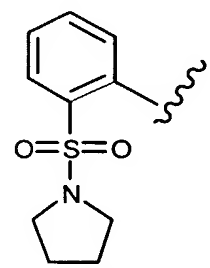
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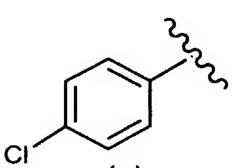
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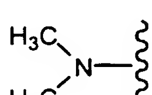
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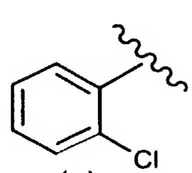
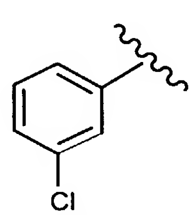

(p) ,

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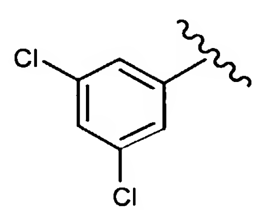
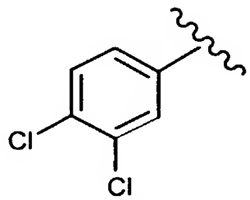
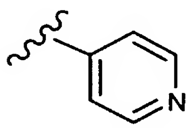

(r) , or

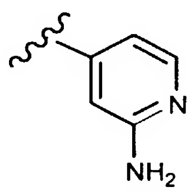


(s) .

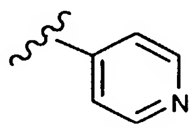
27. The compound of Claim 25 wherein R^2 is selected from:



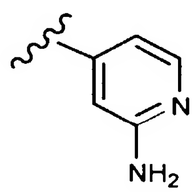
or



28. The compound of Claim 26 wherein R^2 is selected from:



or



29. The compound of Claim 1 selected from: Compound 18, 25, 26, 31, 33, 37, 41, 45, 49, 51, 52, 57, 58 to 67, 73 to 84, 89 to 157, 159 to 168, 212 to 269, 271 to 272, 276 to 282, 284, 285, 287 to 300, 306, 309 to 319, 321 to 336, 338 to 340, 342 to 349, 351 to 361, 363 to 371, 374 to 377, 380 to 383, 387 to 390, 392 to 406, and 408 to 410.

30. The compound of Claim 1 selected from: 93, 276, 306, 317, 331, 332, 333, 336, 366, 343, 366, 367, 374, or 376.

31. The compound of Claim 1 selected from: Compounds 306, 332, 333, 336, 366, 374, or 376.

32. A pharmaceutical composition comprising an effective amount of a compound of Claim 1 and a pharmaceutically effective carrier.

33. A method of treating: allergy, allergy-induced airway responses, congestion, hypotension, cardiovascular disease, hypotension, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo and hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, and migraine comprising administering to a patient in need of such treatment an effective amount of a compound of Claim 1.

34. The method of Claim 33 wherein allergy-induced airway responses are treated.

35. The method of Claim 33 wherein allergy or nasal congestion is treated.

36. A pharmaceutical composition comprising an effective amount of a compound of Claim 1, and an effective amount of H_1 receptor antagonist, and a pharmaceutically effective carrier.

37. A method of treating: allergy, allergy-induced airway responses, and congestion comprising administering to a patient in need of such treatment an effective amount of a compound of Claim 1 in combination with an effective amount of an H_1 receptor antagonist.

38. The method of Claim 37 wherein said H_1 receptor antagonist is selected from:selected from: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.

39. The method of Claim 38 wherein said H_1 receptor antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine or cetirizine.

40. The method of Claim 39 wherein said H_1 receptor antagonist is selected from: loratadine or descarboethoxyloratadine.

41. Use of a compound of Claim 1 for the manufacture of a medicament for treating allergy, allergy-induced airway responses, congestion, hypotension, cardiovascular disease, hypotension, disease of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo and hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, and migraine.

42. Use of a compound of Claim 1 and use of an H_1 receptor atagonist for the manufacture of a medicament for treating allergy, allergy-induced airway responses, congestion, hypotension, cardiovascular disease, hypotension, disease of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo and hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, and migraine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072570 A3

(51) International Patent Classification[7]: C07D 401/14, 401/12, 413/14, 417/14, 498/04, A61K 31/4545, 31/495, A61P 37/08

(21) International Application Number: PCT/US02/07106

(22) International Filing Date: 11 March 2002 (11.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/275,417 13 March 2001 (13.03.2001) US

(71) Applicants: SCHERING CORPORATION [US/US]; Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). PHARMACOPEIA, INC. [US/US]; 3000 Eastpark Boulevard, Cranbury, NJ 08512 (US).

(72) Inventors: ROSENBLUM, Stuart, B.; 16 Steven Terrace, West Orange, NJ 07052 (US). ZENG, Qingbei; 509 Cinder Road, Edison, NJ 08820 (US). MUTAHI, Mwangi, Wa; 45 Snyder Road, Fords, NJ 08863 (US). ASLANIAN, Robert, G.; 144 Philip Drive, Rockaway, NJ 07866 (US). TING, Pauline, C.; 74 Delwick Lane, New Providence, NJ 07974 (US). SHIH, Neng-Yang; 1 Maple Drive, North Caldwell, NJ 07006 (US). SOLOMON, Daniel, M.; 9 Marshall Drive, Edison, NJ 08817 (US). CAO, Jianhua; 203 Country Club Lane, Scotch Plains, NJ 07076 (US). VACCARO, Henry, A.; 123 Somerset Avenue, South Plainfield, NJ 07080 (US). MC CORMICK, Kevin, D.; 5 Pace Drive, Edison, NJ 08820 (US). BALDWIN, John, J.; 621 Gypsy Hill Circle, Gwynedd Valley, PA 19437 (US). LI, Ge; 815 Taolin Road, Building 7, Room 201, LuJiaZui Garden, LuJiaZui, Shanghai (CN).

(74) Agent: JEANETTE, Henry, C.; Schering-Plough Corporation, Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 6 March 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/072570 A3

(54) Title: NON-IMIDAZOLE COMPOUNDS AS HISTAMINE H3 ANTAGONISTS

(57) Abstract: Disclosed are novel compounds of the formula (I). Also disclosed are pharmaceutical compositions comprising the compounds of Formula (I). Also disclosed are methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I). Also disclosed are methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I) in combination with a H1 receptor antagonist.

INTERNATIONAL SEARCH REPORT

ıal Application No
. ., .S 02/07106

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D401/12 C07D413/14 C07D417/14 C07D498/04
A61K31/4545 A61K31/495 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 32893 A (SCHERING CORP) 25 April 2002 (2002-04-25) * see claims 1-40 * the whole document ---	1-42
E	WO 02 072093 A (SCHERING CORP) 19 September 2002 (2002-09-19) * see claims * the whole document ---	1-42
X	US 5 889 006 A (BROWNE MARGARET E ET AL) 30 March 1999 (1999-03-30) * overlap of chemical formula, see the claims * the whole document ---	1-42

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2002	03/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

1

al Application No
I/US 02/07106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 00488 A (MCCOMBIE STUART W ;SCHERING CORP (US); TAGAT JAYARAM R (US); VICE) 6 January 2000 (2000-01-06) * overlap of chemical formula, see the claims * the whole document	1-42
X	WO 98 05292 A (SCHERING CORP) 12 February 1998 (1998-02-12) * overlap of chemical formula, see the claims * the whole document	1-42
Y	WO 99 42446 A (ISHIWATA HIROYUKI ;HATTORI YUKIO (JP); KOWA CO (JP); NAKAO HIROSHI) 26 August 1999 (1999-08-26) * see claims * the whole document	1-42
Y	& EP 1 057 815 A (KOWA CO. LTD.) 6 December 2000 (2000-12-06) * see claim 1, definition of x and Y * the whole document	1-42
Y	STARK H ET AL: "Developments of Histamine H3-receptor Antagonists" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 21, no. 5, 1996, pages 507-520, XP002084872 ISSN: 0377-8282 * see p.512, fig. 7 * the whole document	1-42
Y	GANELLIN,R. ET AL.: "Synthesis of Potent Non-Imidazole Histamine H3 Receptor Antagonists " ARCH.PHARM.PHARM.MED.CHEM., vol. 331, 1998, pages 395-404, XP002123596 WEINHEIM * see p.397, Table 1 * the whole document	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/07106

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the structural limitaiton of claims 8-12 e.g those compounds recited in the examples and closely related homologous compounds.

****************************.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

International Application No
PCT/US 02/07106

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0232893	A	25-04-2002	AU	1535502	A	29-04-2002
			WO	0232893	A2	25-04-2002
WO 02072093	A	19-09-2002	WO	02072093	A2	19-09-2002
			US	2002151565	A1	17-10-2002
US 5889006	A	30-03-1999	US	5883096	A	16-03-1999
			AU	724001	B2	07-09-2000
			AU	3899997	A	25-02-1998
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			CN	1232462	A ,B	20-10-1999
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			EP	0938483	A2	01-09-1999
			HU	9902827	A2	28-08-2000
			JP	2000501117	T	02-02-2000
			KR	2000029947	A	25-05-2000
			NO	990551	A	07-04-1999
			NZ	333801	A	28-04-2000
			PL	331534	A1	19-07-1999
			SK	15599	A3	13-03-2000
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			AU	701452	B2	28-01-1999
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			EP	0811002	A2	10-12-1997
			FI	973446	A	22-10-1997
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			JP	11501014	T	26-01-1999
			NZ	303415	A	28-10-1999
			TW	464646	B	21-11-2001
			WO	9626196	A2	29-08-1996
			ZA	9601293	A	19-08-1996
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			CN	1314905	T	26-09-2001
			EP	1091956	A1	18-04-2001
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